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(54) Title: EXTENDED cDNAs FOR SECRETED PROTEINS

#### (57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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## EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

## Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed
along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.
Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce-false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mischaeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

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portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported 10 sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

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In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- $\alpha$ , interferon- $\beta$ , interferon- $\gamma$ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

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also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., 10 Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

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5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream 15 regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include 20 sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5' coding sequences of genes encoding secretory proteins.

## Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted 25 proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the 30 present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

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portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10<sup>4</sup>-10<sup>6</sup> fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

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cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

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In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the 20 cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

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In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

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The present invention also relates to secretion vectors capable of directing the secretion of a protein of

interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell
which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the 30 preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the full coding sequences of one of SEO ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

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A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

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## **Brief Description of the Drawings**

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and Notl. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the protein of SEO ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEO ID NO: 516).

Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex 10 (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

#### **Detailed Description of the Preferred Embodiment**

## 15 I. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

#### A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

#### **EXAMPLE 1**

## Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1 μg of RNA was incubated in a final reaction medium of 10 μl in the presence of 5 U of  $T_4$  phage RNA ligase in the buffer provided by the manufacturer (Gibco · BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 μl of  $^{32}$ pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH, NaBH, CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

#### **EXAMPLE 2**

## Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

0.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step. Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

+ Cap:

25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)
-Cap:

5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

#### **EXAMPLE 3**

## Coupling of the Dialdehyde with Biotin

The oxidation product obtained in Example 2 was dissolved in 50  $\mu$ l of sodium acetate at a pH of between 5 and 5.2 and 50  $\mu$ l of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n = 5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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## **EXAMPLE 4**

## **Specificity of Biotinylation**

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

- Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as 20 described in Example 1.
  - Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as described in Example 1.
  - Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure.

For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment.

Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

#### **EXAMPLE 5**

## Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

## **EXAMPLE 6**

## 25 <u>Efficiency of Recovery of Biotinylated mRNAs</u>

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with <sup>32</sup>pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

## **EXAMPLE 7**

## Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula H<sub>2</sub>N(R1)NH<sub>2</sub> at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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## **EXAMPLE 8**

## Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100µJ of 0.1N sodium hydroxide, 1.5µg mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

## **EXAMPLE 9**

#### Oxidation of Diols

Up to 1 OD unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

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Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

## **EXAMPLE 10**

## Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

## **EXAMPLE 11**

#### Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO<sub>4</sub>/acetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO<sub>4</sub>/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The
derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step
was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not
joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10  $\mu$ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39  $\mu$ l of 10 mM urea and 2  $\mu$ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45  $\mu$ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µI

fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with 32P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with <sup>32</sup>P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

## alpha-globin

dehydrogenase

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GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5) GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID NO:6) 3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

**Elongation factor E4** 

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (\_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.
  - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the 20 presence of cDNA.
  - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
  - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.
- 25 Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.
  - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of 30 added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEO ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

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oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

## B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

30 groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

#### **EXAMPLE 12**

## Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA+ RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this 10 procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first 15 and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards, supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold 20 Spring Harbor Laboratory Press, 1989.

#### II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

## **EXAMPLE 13**

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## Preparation of mRNA

Total human RNAs or PolyA+ RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by 30 two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

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than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for

enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both
approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an
EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe complementary to the oligonucleotide tag.

#### **EXAMPLE 14**

## cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

20 Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

## **EXAMPLE 15**

## Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

## **EXAMPLE 16**

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

## **EXAMPLE 17**

## Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing

Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

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Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENE<sup>TM</sup> for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL),

25 BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and
peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc.

Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined
match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn30 helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

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Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

#### **EXAMPLE 18**

## Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the 10 sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNA. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the 15 sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to 20 the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S=108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fundal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be 30 identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

#### **EXAMPLE 19**

## Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENE™ database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

## **EXAMPLE 20**

#### Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit  $\alpha$  and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit  $\alpha$  and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the 30 corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENE<sup>TM</sup> database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA

sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

## **EXAMPLE 21**

## Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENE™ was screened to identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

## **EXAMPLE 22**

#### Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENETM contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

#### **EXAMPLE 23**

## Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using
the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequencereporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After
introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be
harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the
medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which
encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

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## Categorization of 5' ESTs Encoding a Signal Pentide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG™ database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

5 Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAGTM database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the 10 known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAG™ database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which 15 extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, 20 as described below in Example 25.

## **EXAMPLE 25**

## **Categorization of Expression Patterns**

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail 30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

#### **EXAMPLE 26**

## **Evaluation of Expression Levels and Patterns of mRNAs**

## Corresponding to 5' ESTs or Extended cDNAs

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Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More 15 preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

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For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are 30 obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides.

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After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density

nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al.

(Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the
5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., supra) or synthesized and then
addressed to the chip (Sosnowski et al., supra). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are
synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

## III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

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The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino acids of the sequences of SEQ ID NOs: 40-140 and

242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

#### **EXAMPLE 27**

## General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENETM database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

## 1. Obtaining Extended cDNAs

#### 10 a) First strand synthesis

The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the
alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra)
matrix as explained in Example 11.

## b) Second strand synthesis

A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

## 5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

#### a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is closed in an appropriate vector such as pED6dpc2, as described in section 3.

#### b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

## c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose

30 primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the 5 length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls 10 and validation steps are carried out as described in example 15.

#### 3. Cloning of Full Length Extended cDNAs

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The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, 30 contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

## 4. Computer Analysis of Full Length Extended cDNA

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Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S=72; identity=70%; and length=40 nucleotides.

- Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ
- 10 (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W=8 and B=10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

#### a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having
more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 90%, were flagged.

b) Identification of structural features

Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it.

The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

#### c) Identification of functional features

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Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

#### d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

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have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs

10 are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E = 0.001.

Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

## 5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

#### a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

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alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

#### b) Manual sequence selection

Manual selection is carried out using automatically generated reports for each sequenced full length extended 5 cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

#### **EXAMPLE 28**

#### Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

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The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID

NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or

functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the
members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in
the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at
http://expasy.hcuge.ch/sprot/prosite.html. Prosite\_convert and prosite\_scan programs
(http://ulrec3.unil.ch/ftpserveur/prosite\_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite\_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

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proteins) was skipped during the search with prosite\_scan. The program used to shuffle protein sequences (db\_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite\_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite\_scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences

10 encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be
obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities
in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

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Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 OJG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

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Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) Preferably, the probe is designed to have a  $T_m$  of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

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The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X106 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu$ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X10s dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

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1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be e.nployed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

**EXAMPLE 29** 

# Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended

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cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

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with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

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sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

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stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

#### IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

30 EXAMPLE 30

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## Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

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peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

5 It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377. 10 For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides 15 comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEO ID NOs: 40-140 and 242-377 as defined in Table IV above.

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It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

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listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

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The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5'primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with Pstl, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with Bgl II.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

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Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

(Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express<sup>TM</sup> Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

#### **EXAMPLE 31**

20 <u>Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface</u>

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various

amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the
cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an
unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein
bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled
protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

#### 5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in **Current Protocols in Immunology**. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. **Current Protocols in**Immunology., *supra* Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

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The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 33**

# Assaying the Proteins Expressed from Extended cDNAs or Portions

#### Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al.; J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation
of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264,
10 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins encoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

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myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

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tolerizing agent.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 20 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4lg fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

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of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which 5 promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

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Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

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The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β2 macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain,can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 34**

# <u>Assaving the Proteins Expressed from Extended cDNAs</u> or <u>Portions Thereof for Hematopoiesis Regulating Activity</u>

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

## **EXAMPLE 35**

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

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nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and 5 other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

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Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

30 The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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#### **EXAMPLE 36**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 36A**

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## Assaying the Proteins Expressed from Extended cDNAs or

## Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

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Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

#### **EXAMPLE 37**

# Assaying the Proteins Expressed from Extended cDNAs or

#### Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 38**

# Assaying the Proteins Expressed from Extended cDNAs or

# Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

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molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

#### **EXAMPLE 38A**

## Assaying the Proteins Expressed from Extended cDNAs or Portions

#### Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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#### **EXAMPLE 38B**

# Assaying the Proteins Expressed from Extended cDNAs or

## Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### **EXAMPLE 39**

# Identification of Proteins which Interact with

#### Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof

are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes.

30 The oocytes are then assayed for a desired acitivity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

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Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended

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cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase.

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5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column.

Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can

be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

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Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

#### **EXAMPLE 40**

## Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

# A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

# B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

# V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

#### **EXAMPLE 41**

# Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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#### **EXAMPLE 42**

## Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

#### **EXAMPLE 43**

#### Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

#### **EXAMPLE 44**

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## Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

#### **EXAMPLE 45**

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#### Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., <a href="mailto:supra">supra</a>). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

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nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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#### **EXAMPLE 46**

#### **Dot Blot Identification Procedure**

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P32 using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 12P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

### **EXAMPLE 47**

## Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P<sup>32</sup>. The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species 20 from which a sample is derived as described above.

#### **EXAMPLE 48**

## Identification of Tissue Types or Cell Species by Means of

#### Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that
reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

## A. Immunohistochemical Techniques

Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 1251, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

## B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 µl, and containing from about 1 to 100 µg protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or mora specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

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The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

#### **EXAMPLE 49**

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr.idine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

#### **EXAMPLE 50**

## Mapping of Extended cDNAs to Human

## Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron.

Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see

Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 µCu of a <sup>32</sup>P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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#### **EXAMPLE 51**

### Mapping of Extended 5' ESTs to Chromosomes

#### Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. *VProc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µg/ml) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research

Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at  $\cdot 20^{\circ}$ C are treated for 1 h at 37°C with RNase A (100  $\mu$ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl<sub>2</sub>) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of
5 biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., *supra.*). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given
10 chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

#### **EXAMPLE 52**

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## Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms 30 chromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

## **EXAMPLE 53**

Identification of genes associated with hereditary diseases or drug response

This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

## VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

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## **EXAMPLE 54**

## **Construction of Secretion Vectors**

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the

extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion 5 protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including 10 retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange 20 chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is 25 desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and 30 other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

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## Use of Extended cDNAs or 5' ESTs to Clone Upstream

#### Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the 5 GenomeWalker™ kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or ' EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5  $\mu$ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2  $\mu$ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of  $Mg(OAc)_2$ , and 1  $\mu$ l of the Tth polymerase 50X mix in a total volume of 50  $\mu$ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5  $\mu$ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50  $\mu$ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

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In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

### **EXAMPLE 56**

### Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pBgal-Basic, pBgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase,  $oldsymbol{eta}$ galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

### **EXAMPLE 57**

Cloning and Identification of Promoters

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Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

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Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

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Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

## **EXAMPLE 58**

# Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K 1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

# VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

EXAMPLE 59

## Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

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The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10<sup>-10</sup>M to 1x10<sup>-4</sup>M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10<sup>-7</sup> translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., supra.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the

effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to
antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

## **EXAMPLE 60**

## Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as

Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target
gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based
upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived
with known gene sequences that have been associated with a particular function. The cell functions can also be

predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

#### **EXAMPLE 61**

## Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

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## **EXAMPLE 62**

## Use Of Signal Peptides Encoded By 5' Ests Or Sequences

## Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

## **EXAMPLE 63**

## Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

## 25

#### **EXAMPLE 64**

#### Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 33) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed agains; the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

# 15 A) Proteins which are closely related to known proteins

## Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

## 25 Proteins of SEQ ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs.. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs:175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

## 5 Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

#### 20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic 30 shock.

## Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex elF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8: 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

## Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi *et al., FEBS Lett.*, 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink *et al., Hum. Mol. Gent.*, 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

<u>Proteins of SEQ ID NOs: 149, 150 and 211</u>

The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response.

Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

### Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably
of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders
including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

## Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AFO19225). The matched protein is a secreted high density lipoprotein associated with apoA-I-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

## Protein of SEQ ID NO: 163

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The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

## C) Proteins homologous to a domain of a protein with known function

## Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

### Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369: 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

## Protein of SEQ ID NO: 153

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The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction
and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

#### Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

## Protein of SEQ ED NO: 240

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The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

### Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

## Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

## Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEQ ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

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types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

### Protein of SEQ ED NO: 167

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The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEQ ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

## Protein of SEQ ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

15 homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

### 25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily. The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other 25 protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing 30 such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

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# SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing:

In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

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TABLE I

		•
SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	82
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	81
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	53
51	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
52	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
53	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
54	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
56	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
57	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
60	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
61	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
62	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	69
63	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	49
64	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
65	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	53
66	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	57
67	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	54
68	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	55
69	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	58
70	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	59

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TABLE II : Parameters used for each step of EST analysis

		Search Charac	cteristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S=61 X=16	90	17
tRNA	Fasta	both	•	80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S=108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S-144	90	40
Alu	fasta*	both	•	70	40
L1	Blastn	both	S-72	70	40
Repeats	Biastn	both	S=72	70	40
Promoters	Blastn	top	S-54 X-16	90	15⊥
Vertebrate	fasta*	both	S-108	90	30
ESTs	Blatsn	both	S-108 X-16	90	30
Proteins	blastxn	top	E-0.001	· .	<del>- :</del>

<sup>\*</sup> use "Quick Fast" Database Scanner

 $oldsymbol{\perp}$  alignment further constrained to begin closer than 10bp to EST\5' end

 $<sup>5~\</sup>eta~using~BLOSUM62~substitution~matrix$ 

TABLE III: Parameters used for each step of extended cDNA analysis

	Search characte	ristics	Selection characteristics			:s
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous •	FASTA	both		90	15	
tRNA*	FASTA	both	•	80	90	<del></del>
rRNA*	BLASTN	both	S-108	80	40	
mtRNA*	BLASTN	both	S-108	80	40	
Procaryotic*	BLASTN	both	S-144	90	40	
Fungal*	BLASTN	both	S-144	90	40	
Alu*	BLASTN	both	S-72	70	40	max 5 matches, masking
L11	BLASTN	both	S-72	70	40	max 5 matches, masking
Repeats*	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides
Polyadenylati on signal		top	AATAAA allowing 1 mis	match		in the 50 nucleotides preceding the 5' end of the polA
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching sequences
ESTs*	BLAST2N	both		90	30	
Geneseq	BLASTN	both	W-8, B-10	90	30	
ORF	BLASTP	top	W-8, B-10	•	•	on ORF proteins, max 10 matches
Proteins*	BLASTX	top	E-0.001	70	30	

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

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**TABLE IV** 

ld	FCS Location	SigPep Location	ľ	Stop	PolyA Signal	PolyA Site Location
			Polypeptide	Codon	Location	j
40	7 through 471	7 through 99	Location 100 through 471	Location 472	537 through 542	554 through 568
41	168 through 332		168 through 332	333	557 through 562	
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614		
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041		2024 through 2036
46	443 through 619	443 through 589	590 through 619	620	1.	1267 through 1276
47	206 through 747	1	206 through 747	<del>                                     </del>		
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41	1.	21 through 41	42	328 through 333	357 through 370
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994
52	271 through 399		271 through 399	400		·
53	103 through 252	103 through 213	214 through 252	253	· ·	588 through 597
54	2 through 460		2 through 460	461	713 through 718	735 through 748
55	31 through 231		31 through 231	232	769 through 774	690 through 703
56	305 through 565		305 through 565	566	694 through 699	713 through 725
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705
58	135 through 206		135 through 206	207	850 through 855	1056 through 1069
59	135 through 818	·	135 through 818	819	909 through 914	1071 through 1084
60	33 through 290	33 through 92	93 through 290	291		
61	485 through 616		485 through 616	617		669 through 682
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312	•	
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
69	2 through 757	2 through 205	206 through 757	758		1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
73	62 through 916	62 through 757	758 through 916			904 through 916
74	62 through 520		62 through 520	521	1124 through 1129	1141 through 1153
75	21 through 167		21 through 167	168		
76	22 through 318	22 through 93	94 through 318		497 through 502	516 through 526
77	8 through 292		119 through 292		317 through 322	339 through 352
78	16 through 378		85 through 378		502 through 507	ood undugit odz

CONT. TABLE IV

CON	T. TABLE IV					
79	57 through 233	· -	57 through 233	· _	·	
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542		597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382	· -	89 through 382	383	•	408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362		
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802	•	199 through 802		780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361	•	26 through 361	1.	•	350 through 361
92	3 through 131	•	3 through 131	132		591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417	-	327 through 417	ļ. —		404 through 417
97	63 through 398	63 through 206	207 through 398	399	•	
98	2 through 163		2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466		
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295		
102	81 through 518	81 through 173	174 through 518	519		
103	66 through 326	•	66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290		•
105	36 through 497		36 through 497	498	650 through 655	663 through 685
106	18 through 320		18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333	·	702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563		
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400		
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	
119	44 through 505	44 through 223	224 through 505	506		
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770
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CONT. TABLE IV

COV	IT. TABLE IV					
121	58 through 1095	58 through 114	115 through 1095	1096	·	1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659		440 through 659	1.	601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	·
128	121 through 477	121 through 288	289 through 477			·
129	2 through 163	-	2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62.through 385	j.	62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551		714 through 725
133	124 through 231	1.	124 through 231	232		387 through 400
134	131 through 1053	131 through 169	170 through 1053	1-	1019 through 1024	·
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382	·	875 through 886
138	46 through 579	46 through 156	157 through 579	580	•	•
139	92 through 471	92 through 172	173 through 471	·	454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559		1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674		1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263	263 through 481	263 through 322	323 through 481	482		858 through 868
					·	

CONT. TABLE IV

264       42 through 299       42 through 299       300       .       762 through 772         265       198 through 431       198 through 260       261 through 431       432       .       1064 through 11         266       279 through 473       279 through 362       363 through 473       474       944 through 949       970 through 98         267       12 through 644       12 through 92       93 through 644       645       1002 through 1007       1020 through 10         268       91 through 459       91 through 330       331 through 459       460       .       1271 through 174         269       70 through 327       70 through 147       148 through 327       328       1741 through 1746       1763 through 17         270       12 through 497       12 through 104       105 through 497       498       935 through 940       955 through 967         271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 774       761 through 773         273       43 through 221       43 through 177       178 through 222       233       530 through 535       555 through 566
266       279 through 473       279 through 362       363 through 473       474       944 through 949       970 through 98         267       12 through 644       12 through 92       93 through 644       645       1002 through 1007       1020 through 10         268       91 through 459       91 through 330       331 through 459       460       .       1271 through 12         269       70 through 327       70 through 147       148 through 497       328       1741 through 1746       1763 through 17         270       12 through 497       12 through 497       498       935 through 940       955 through 967         271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 384       232 through 380       301 through 384       385       650 through 655       662 through 673         276       143 through 463       294 through 379       380 through 463       464       .       . <t< td=""></t<>
267       12 through 644       12 through 92       93 through 644       645       1002 through 1007       1020 through 10         268       91 through 459       91 through 330       331 through 459       460       -       1271 through 12         269       70 through 327       70 through 147       148 through 327       328       1741 through 1746       1763 through 17         270       12 through 497       12 through 104       105 through 497       498       935 through 940       955 through 967         271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 180       181 through 221       223       530 through 535       555 through 566         274       115 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         275       232 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         276       143 through 463       284 through 379       380 through 671       672
268       91 through 459       91 through 330       331 through 459       460       -       1271 through 12         269       70 through 327       70 through 147       148 through 327       328       1741 through 1746       1763 through 17         270       12 through 497       12 through 104       105 through 497       498       935 through 940       955 through 967         271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 379       380 through 463       464       -       762 through 772         278       162 through 671       162 through 398       399 through 632       633       808 through
269       70 through 327       70 through 147       148 through 327       328       1741 through 1746       1763 through 17         270       12 through 497       12 through 104       105 through 497       498       935 through 940       955 through 967         271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 379       380 through 427       428       606 through 611       628 through 639         277       284 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633
270       12 through 497       12 through 104       105 through 497       498       935 through 940       955 through 967         271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       284 through 379       380 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633       808 through 813       829 through 840
271       90 through 383       90 through 200       201 through 383       384       609 through 614       632 through 643         272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       284 through 379       380 through 463       464       -       762 through 772         278       162 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 632       63 through 632       63 through 813       829 through 840
272       332 through 541       332 through 376       377 through 541       542       739 through 744       761 through 773         273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       294 through 379       380 through 463       464       -       762 through 772         278       162 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633       808 through 813       829 through 840
273       43 through 222       43 through 177       178 through 222       223       530 through 535       555 through 566         274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       294 through 379       380 through 463       464       -       762 through 772         278       162 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633       808 through 813       829 through 840
274       115 through 231       115 through 180       181 through 231       232       419 through 424       445 through 455         275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       284 through 379       380 through 463       464       .       762 through 772         278       162 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633       808 through 813       829 through 840
275       232 through 384       232 through 300       301 through 384       385       650 through 655       662 through 673         276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       294 through 379       380 through 463       464       -       762 through 772         278       162 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633       808 through 813       829 through 840
276       143 through 427       143 through 286       287 through 427       428       606 through 611       628 through 639         277       284 through 463       294 through 379       380 through 463       464       -       762 through 772         278       162 through 671       162 through 398       399 through 671       672       805 through 810       830 through 840         279       63 through 632       63 through 308       309 through 632       633       808 through 813       829 through 840
277     284 through 463     294 through 379     380 through 463     464     -     762 through 772       278     162 through 671     162 through 398     399 through 671     672     805 through 810     830 through 840       279     63 through 632     63 through 308     309 through 632     633     808 through 813     829 through 840
278     162 through 671     162 through 398     399 through 671     672     805 through 810     830 through 840       279     63 through 632     63 through 308     309 through 632     633     808 through 813     829 through 840
279 63 through 632 63 through 308 309 through 632 633 808 through 813 829 through 840
200 23 45 202 204 202 204 202 203 203 204 203 204 205 204 205 2
200 21 through 202 21 through 200 200 through 200 200 through 200 200 200 through 200 200 200 200 200 200 200 200 200 20
280   21 through 362   21 through 200   201 through 362   363   821 through 826   838 through 849
281 21 through 503 21 through 344 345 through 503 504 1305 through 1310 1330 through 134
282 1 through 201 1 through 63 64 through 201 202 637 through 642 660 through 671
283 39 through 1034 39 through 134 135 through 1034 1035 1566 through 1571 1587 through 159
284 69 through 263 69 through 125 126 through 263 264 1173 through 1178 1196 through 120
285 115 through 285 115 through 204 205 through 285 286 505 through 510 525 through 536
286 90 through 344 90 through 140 141 through 344 345 500 through 505 515 through 527
287 57 through 311 57 through 107 108 through 311 312 467 through 472 482 through 493
288 96 through 302 96 through 182 183 through 302 303 - 501 through 514
289   161 through 526   161 through 328   329 through 526   527   .     799 through 811
290 210 through 332 210 through 299 300 through 332 333 594 through 599 613 through 625
291 212 through 361 212 through 319 320 through 361 362 650 through 655 673 through 684
292 75 through 482 75 through 128 129 through 482 483 595 through 600 618 through 627
293 50 through 631 50 through 244 245 through 631 632 777 through 782 801 through 812
294 154 through 576 154 through 360 361 through 576 577 737 through 742 763 through 775
295 154 through 897 154 through 360 361 through 897 898 1017 through 1022 1044 through 105
296   146 through 292   146 through 253   254 through 292   293   395 through 400   433 through 444
297   126 through 383   126 through 167   168 through 383   384   726 through 731   743 through 754
298 66 through 497 66 through 239 240 through 497 498 594 through 599 618 through 629
299 49 through 411 49 through 96 97 through 411 412 732 through 737 750 through 763
300 49 through 534 49 through 96 97 through 534 535 593 through 598 612 through 623
301 86 through 415 86 through 145 146 through 415 416 540 through 545 560 through 571
302 56 through 268 56 through 100 101 through 268 269 584 through 589 601 through 612
303 32 through 328 32 through 103 104 through 328 329 508 through 513 528 through 539
304 21 through 527 21 through 95 96 through 527 528 921 through 926 953 through 963
305 147 through 647 147 through 374 375 through 647 648 . 668 through 681

CONT. TABLE IV

CO	NT. TABLE IV					
30	6 262 through 471	262 through 306	307 through 471	472	663 through 668	682 through 693
307	7 74 through 1216	74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
308	48 through 164	48 through 89	90 through 164	165	482 through 487	505 through 517
309	185 through 334	185 through 295	296 through 334	335	355 through 360	392 through 405
310	195 through 347	195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
311	90 through 815	90 through 179	180 through 815	816	883 through 888	905 through 916
312	52 through 513	52 through 231	232 through 513	514	553 through 558	572 through 583
313	172 through 438	172 through 354	355 through 438	439	682 through 687	685 through 697
314	148 through 366	148 through 225	226 through 366	367	770 through 775	792 through 803
315	175 through 336	175 through 276	277 through 336	337	·	812 through 823
316	191 through 553	191 through 304	305 through 553	554	766 through 771	804 through 817
317	106 through 603	106 through 216	217 through 603	604		1102 through 1112
318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
320	44 through 814	44 through 112	113 through 814	815	1.	978 through 989
321	3 through 581	3 through 182	183 through 581	582	1.	1006 through 1016
322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
324	201 through 332	201 through 251	252 through 332	333		869 through 880
325	217 through 543	217 through 255	256 through 543	544	1.	1206 through 1217
326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
331	672 through 752	672 through 722	723 through 752	753		1150 through 1161
332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645
334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400
335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
336	54 through 590	54 through 227	228 through 590	591		955 through 965
337	133 through 846	133 through 345	346 through 846	847		890 through 901
338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347
339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983
340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745
341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106
342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190
343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070
344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213
345	86 through 709	86 through 361	362 through 709	710	943 through 948	963 through 973
346	63 through 320	63 through 179	180 through 320	321	771 through 776	799 through 810
347	299 through 418	299 through 379	380 through 418	419	739 through 744	762 through 771
		····				

CONT. TABLE IV

_ 60	NI. IABLE IV					
348	186 through 380	186 through 233	234 through 380	381	383 through 388	396 through 409
349	69 through 458	69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340	1.	1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326	T	718 through 729
355	78 through 731	78 through 227	228 through 731	732		1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
357	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949		1016 through 1028
360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
361	628 through 804	628 through 711	712 through 804	805	1.	864 through 875
362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
364	111 through 434	111 through 185	186 through 434	435		618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613	•	839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	633 through 644
369	9 through 185	9 through 50	51 through 185	186		906 through 918
370	14 through 316	14 through 121	122 through 316	317	442 through 447	458 through 471
371	70 through 1092	70 through 234	235 through 1092	1093	1475 through 1480	1493 through 1504
372	274 through 597	274 through 399	400 through 597	598	731 through 736	754 through 765
373	230 through 469	230 through 307	308 through 469	470	1004 through 1009	1027 through 1040
374	72 through 545	72 through 203	204 through 545	546		1151 through 1162
375	36 through 425	36 through 119	120 through 425	426	1215 through 1220	1240 through 1250
376	155 through 751	155 through 340	341 through 751	752	912 through 917	937 through 947
377	46 through 585	46 through 120	121 through 585	586	584 through 589	606 through 619
						ı • I

TABLE V

		INDIL V	
ld	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55	•	1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180	<u> </u>	1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	1 through 97
151	1 through 7		1 through 7
152	-42 through 157	-42 through -1	1 through 157
153	1 through 43	·	1 through 43
154	-37 through 13	-37 through -1	1 through 13
155	1 through 153		1 through 153
156	1 through 67	·	1 through 67
157	1 through 87		1 through 87
158	-85 through 165	-85 through -1	1 through 165
159	1 through 24	•	1 through 24
160	1 through 228	•	1 through 228
161	-20 through 66	-20 through -1	1 through 66
162	1 through 44	-	1 through 44
163	-58 through 256	-58 through -1	1 through 256
164	-80 through 9	-80 through -1	1 through 9
165	15 through 83	-15 through -1	1 through 83
166	-36 through 56	-36 through -1	1 through 56
167	-16 through 335	-16 through -1	1 through 335
168	-47 through 91	-47 through -1	1 through 91
169	-73 through 28	-73 through -1	1 through 28
170	-68 through 184	-68 through -1	1 through 184
171	-68 through 282	-68 through -1	1 through 282
172	-68 through 322	-68 through -1	1 through 322
173	-82 through 108	-82 through -1	1 through 108
174	-232 through 53	-232 through -1	1 through 53
175	1 through 153	•	1 through 153
176	1 through 49	· · · · · · · · · · · · · · · · · · ·	1 through 49
177	-24 through 75	-24 through -1	1 through 75
178	37 through 58	-37 through -1	1 through 58
179	-23 through 98	-23 through -1	1 through 98
180	1 through 59		1 through 59
181	-14 through 72	-14 through -1	1 through 72
182	-58 through 107	-58 through -1	1 through 107
183	-35 through 45	-35 through -1	1 through 45
184	-21 through 52	-21 through -1	1 through 52
185	1 through 98		1 through 98
186	-21 through 91	-21 through -1	1 through 91
187	-44 through 26	-44 through -1	1 through 26
188	-13 through 79	-13 through -1	1 through 79
189	-42 through 165	-42 through -1	1 through 165
190	1 through 201	·	1 through 201

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CONT. TABLE V

191	-37 through 342	-37 through -1	1 through 342
192	1 through 112		1 through 342
193	1 through 43		1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	
197	1 through 30	·	1 through 319
198	-48 through 64	-48 through -1	1 through 30 1 through 64
199	1 through 54	·	
200	-21 through 130	-21 through -1	1 through 54
201	-25 through 203	-25 through -1	1 through 130
202	-47 through 17	-47 through -1	1 through 203
203	-31 through 115	-31 through -1	1 through 17
204	1 through 87	or through -1	1 through 115
205	-27 through 13	-27 through -1	1 through 87
206	1 through 154	27 through 1	1 through 13
207	1 through 101		1 through 154
208	-22 through 434	-22 through -1	1 through 101
209	-17 through 81	-17 through -1	1 through 434
210	-29 through 54	-29 through -1	1 through 81
211	-23 through 206	-23 through -1	1 through 54
212	-21 through 131	-23 through -1	1 through 206
213	-54 through 125		1 through 131
214	-92 through 177	-54 through -1 -92 through -1	1 through 125
215	-22 through 113		1 through 177
216	-38 through 29	-22 through -1 -38 through -1	1 through 113
217	-54 through 71		1 through 29
218	-21 through 355	-54 through -1	1 through 71
219	-30 through 181	-21 through -1	1 through 355
220	-60 through 94	-30 through -1 -60 through -1	1 through 181
221	-42 through 81		1 through 94
222	-19 through 327	-42 through -1	1 through 81
223	-20 through 190	-19 through -1	1 through 327
224	-20 through 164	-20 through -1	1 through 190
225	-22 through 205	-20 through -1	1 through 164
226	-41 through 33	-22 through -1	1 through 205
227	1 through 73	-41 through -1	1 through 33
228	-16 through 66	16 4	1 through 73
229	-56 through 63	-16 through -1	1 through 66
230	1 through 54	-56 through -1	1 through 63
231	-14 through 196	14 4 5	1 through 54
232	1 through 108	-14 through -1	1 through 196
233	-18 through 25	10 shows 1	1 through 108
234	1 through 36	-18 through -1	1 through 25
235	-13 through 294		1 through 36
236	-32 through 74	-13 through -1	1 through 294
237	-19 through 23	·32 through ·1	1 through 74
238		-19 through -1	1 through 23
239	-20 through 97	-20 through -1	1 through 97
40	-37 through 141	-37 through -1	1 through 141
41	-27 through 99	-27 through -1	1 through 99
78	-115 through 59	-115 through -1	1 through 59
	-20 through 32	-20 through -1	1 through 32
79 80	-23 through 170	-23 through -1	1 through 170
00	-14 through 68	-14 through -1	1 through 68

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CONT. TABLE V

ONT. TABLE V	•		
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	-18 through -1	1 through 42
397	-93 through 99	-93 through -1	1 through 99
398	-72 through 77	-72 through -1	1 through 77
399	-20 through 53	-20 through -1	1 through 53
400	-20 through 66	-20 through -1	1 through 66
401	-21 through 57	-21 through -1	1 through 57
402	-28 through 37	-28 through -1	1 through 37
403	-27 through 184	-27 through -1	1 through 184
404	-80 through 43	-80 through -1	1 through 43
405	-26 through 60	-26 through -1	1 through 60
406	-31 through 131	-31 through -1	1 through 131
407	-37 through 61	-37 through -1	1 through 61
408	-15 through 55	-15 through -1	1 through 55
409	-45 through 15	-45 through -1	1 through 15
410	-22 through 17	-22 through -1	1 through 17
411	-23 through 28	-23 through -1	1 through 28
412	-48 through 47	-48 through -1	1 through 47
413	-32 through 28	-32 through -1	1 through 28
414	-79 through 91	·79 through -1	1 through 91
415	-82 through 108	-82 through -1	1 through 108
416	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
418	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
420	-19 through 46	-19 through -1	1 through 46
422	-30 through 27	-30 through -1	1 through 27
423	-17 through 68	-17 through -1	1 through 68
424	-17 through 68	-17 through -1	1 through 68
425	-29 through 40	-29 through -1	1 through 40
426	-56 through 66	-56 through -1	1 through 66
427	-30 through 11	-30 through -1	1 through 11
428	-36 through 14	-36 through -1	1 through 14
429	-18 through 118	-18 through -1	1 through 118
430	-65 through 129	-65 through -1	1 through 129
431	-69 through 72	-69 through -1	1 through 72
432	-69 through 179	-69 through -1	1 through 179
433	-36 through 13	-36 through -1	1 through 13
434	-14 through 72	-14 through -1	1 through 72
435	-58 through 86	-58 through -1	1 through 86
	<del> </del>		Jugii 00

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CONT. TABLE V

CONT. TABL	.E <sub>.</sub> V		
436	-16 through 105	-16 through -1	1 through 105
437	·16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	-76 through 91	-76 through -1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	-14 through 25	-14 through -1	1 through 25
446	-37 through 13	-37 through -1	1 through 13
447	-26 through 25	·26 through -1	1 through 25
448	-30 through 212	-30 through -1	1 through 212
449	-60 through 94	-60 through -1	1 through 94
450	-61 through 28	-61 through -1	1 through 28
451	-26 through 47	·26 through ·1	1 through 47
452	-34 through 20	-34 through -1	
453	-38 through 83	-38 through -1	1 through 20
454	-37 through 129	-37 through -1	1 through 83 1 through 129
455	-26 through 154	-26 through -1	· · · · · · · · · · · · · · · · · · ·
456	-64 through 27	-64 through -1	1 through 154
457	-23 through 234	-23 through -1	1 through 27
458	-60 through 133	-60 through -1	1 through 234
459	-28 through 79	-28 through -1	1 through 133
460	-13 through 108	-13 through -1	1 through 79
461	-17 through 27	-17 through -1	1 through 108
462	-13 through 96		1 through 27
463	-41 through 102	-13 through -1 -41 through -1	1 through 96
464	-30 through 202	-30 through -1	1 through 102
465	-21 through 40	-21 through -1	1 through 202
466	-19 through 15	-19 through -1	1 through 40
467	-54 through 161	-54 through -1	1 through 15
468	-17 through 10		1 through 161
469	-24 through 61	-17 through -1	1 through 10
470	-16 through 35	-24 through -1	1 through 61
471	-43 through 24	-16 through -1	1 through 35
472	-15 through 48	-43 through -1	1 through 24
473		-15 through -1	1 through 48
474	-58 through 121 -71 through 167	-58 through -1	1 through 121
475	-37 through 141	-71 through -1	1 through 167
476	-21 through 75	-37 through -1	1 through 141
477	-21 through 75	-21 through -1	1 through 75
477		-24 through -1	1 through 17
479	-27 through 86 -18 through 232	-27 through -1	1 through 86
480		-18 through -1	1 through 232
481	-21 through 130	-21 through -1	1 through 130
	-25 through 214	-25 through -1	1 through 214
482 483	-92 through 116	-92 through -1	1 through 116
	-39 through 47	-39 through -1	1 through 47
484	-27 through 13	-27 through -1	1 through 13
485	-16 through 49	-16 through -1	1 through 49
486	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	. 1 through 15

490	-52 through 111	-52 through -1	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
491	-47 through 17	-47 through -1	1 through 111
492	-50 through 168	-50 through -1	1 through 17
493	-15 through 201		1 through 168
494	-19 through 115	-15 through -1	1 through 201
495	-16 through 69	-19 through -1	1 through 115
496	-29 through 263	-16 through -1	1 through 69
497	· · · · · · · · · · · · · · · · ·	-29 through -1	1 through 263
498	56 through 66	-56 through -1	1 through 66
499	-28 through 31	-28 through -1	1 through 31
500	-13 through 86	-13 through -1	1 through 86
	-13 through 86	-13 through -1	1 through 86
501	-25 through 83	-25 through -1	1 through 83
502	-15 through 168	-15 through -1	1 through 168
503	-15 through 83	-15 through -1	1 through 83
504	-57 through 126	-57 through -1	1 through 126
505	-14 through 126	-14 through -1	1 through 126
506	-14 through 45	-14 through -1	1 through 45
507	-36 through 65	-36 through -1	
508	-55 through 286	-55 through -1	1 through 65
509	-42 through 66	-42 through -1	1 through 286
510	-26 through 54	-26 through -1	1 through 66
511	-44 through 114	-44 through -1	1 through 54
512	-28 through 102		1 through 114
513	-62 through 137	-28 through -1	1 through 102
514	·25 through 155	-62 through -1	1 through 137
	20 1110111 133	-25 through -1	1 through 155

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# TABLE VI

ld	Collection refs	Deposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 98921	SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
6	ATCC # 98920	SignalTag 67-90
7	ATCC # 98921	SignalTag 121-144
58	ATCC # 98920	SignalTag 67-90
59	ATCC # 98920	SignalTag 67-90
0	ATCC # 98920	SignalTag 67-90
1	ATCC # 98923	SignalTag 44-66
2	ATCC # 98923	SignalTag 44-66
3	ATCC # 98923	SignalTag 44-66
4	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
5	ATCC # 98923	SignalTag 44-66
6	ATCC # 98921	SignalTag 121-144
7	ATCC # 98920	SignalTag 67-90
3	ATCC # 98920	SignalTag 67-90
)	ATCC # 98921	SignalTag 121-144
)	ATCC # 98921	SignalTag 121-144
	ATCC # 98921	SignalTag 121-144
	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
	ATCC # 98923	SignalTag 44-66

74	ATCC # 98923	SignalTag 44-66
75	ATCC # 98920	SignalTag 67-90
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
78	ATCC # 98921	SignalTag 121-144
79	ATCC # 98923	SignalTag 44-66
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
81	ATCC # 98921	SignalTag 121-144
82	ATCC # 98920	SignalTag 67-90
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
84	ATCC # 98923	SignalTag 44-66
85	ATCC # 98923	SignalTag 44-66
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
87	ATCC # 98923	SignalTag 44-66
88	ATCC # 98923	SignalTag 44-66
89	ATCC # 98923	SignalTag 44-66
90	ATCC # 98923	SignalTag 44-66
91	ATCC # 98923	SignalTag 44-66
92	ATCC # 98920	SignalTag 67-90
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
94	ATCC # 98923	SignalTag 44-66
95	ATCC # 98923	SignalTag 44-66
96	ATCC # 98920	SignalTag 67-90
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
98	ATCC # 98921	SignalTag 121-144
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
100	ATCC # 98921	SignalTag 121-144
101	ATCC # 98920	SignalTag 67-90
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
105	ATCC # 98921	SignalTag 121-144
06	ATCC # 98920	SignalTag 67-90
07	ATCC # 98920	SignalTag 67-90
08	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
09	ATCC # 98923	SignalTag 44-66
10	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120

111	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120.
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
139	ECACC # 98121506	SignalTag 11121998
140	ECACC # 98121506	SignalTag 11121998

-123-TABLE VII

Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CL0_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22·11·2·H9·CL1_1	43	DNA
25-7-3-D4-CLO_2	44	DNA
26-27-3-D7-CLO_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
` 26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CLO_1	48	DNA
27-1-2-B3-CLO_2	49	DNA
27-19-3-G7-CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	-65	DNA
47-14-1-C3-CL0_5	66	DNA
47-15-1-E11-CLO_1	67	DNA
47-15-1-H8-CLO_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48-1-1-H7-CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2 1	73	DNA

48-54-1-G9-CL3_1	74	DNA
48-7-4-H2-CL2_2	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-69-CLD_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CL0_2	82	DNA
51-34-3-F8-CLO_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	87	DNA
58-34-3-C9-CL1_2	88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CLO_1	98	DNA
77-16-4-G3-CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CLO_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CLO_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CLO_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CLO_3	110	DNA

30-12-3-G5-CL0_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CL0_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CLO_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CL0_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT

26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CL0_5	167	PRT
47-15-1-E11-CL0_1	168	PRT
47-15-1-H8-CLO_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CLO_5	172	PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51-15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRT
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CL0_2	183	PRT
51-34-3-F8-CLO 2	184	PRT

57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
√ 65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CLO_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CL0_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CLO_3	211	PRT
30-12-3-G5-CL0_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CL0_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CL0_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CL0_4	221	PRT

57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224	PRT
78-8-3-E6-CL0_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33-11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLO_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CLO_1	233	PRT
55-1-3-D11-CLO_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT
78-21-3-G7-CL2_1	240	PRT
58-45-4-B11-CL13_2	241	PRT
20-6-1-D11-FL2	242	DNA
20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1-G11-FL1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
33-14-4-E1-FL1	256	DNA
33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA

33-27-1-E11-FL1	259	DNA
33-28-4-D1-FL1	260	DNA
33-28-4-E2-FL2	261	DNA
33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-87-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-G4-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
48-8-1-D8-FL3	283	DNA
48-13-3-H8-FL1	284	DNA
48-19-3-A7-FL1	285	DNA
48-19-3-G1-FL1	286	DNA
48-25-4-D8-FL1	287	DNA
48-21-4-H4-FL1	288	DNA
48-26-3-B8-FL2	289	DNA
48-29-1-E2-FL1	290	DNA
48-31-3-F7-FL1	291	DNA
48-47-3-A5-FL1	292	DNA
51-1-1-G12-FL1	293	DNA
51-1-4-E9-FL3	294	DNA
51-1-4-E9-FL2	295	DNA

51-2-1-E10-FL1	296	DNA
51-2-3-F10-FL1	297	DNA
51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
51-3-3-B10-FL3	300	DNA
51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
51-15-4-H10-FL1	305	DNA
51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
55-1-3-H10-FL1	314	DNA
55-5-4-A6-FL1	315	DNA
58-26-3-D1-FL1	316	DNA
57-18-1-D5-FL1	317	DNA
57-27-3-A11-FL1	318	DNA
57-27-3-G10-FL2	319	DNA
58-10-3-D12-FL1	320	DNA
58-11-1-G10-FL1	321	DNA
58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
58-38-1-A2-FL2	324	DNA
58-38-1-E5-FL1	325	DNA
58-44-2-B3-FL3	326	DNA
58-45-3-H11-FL1	327	DNA
58-53-2-B12-FL2	328	DNA
59-9-4-A10-FL1	329	DNA
60-16-3-A6-FL1	330	DNA
60-17-3-G8-FL2	331	DNA
62-5-4-B10-FL1	332	DNA

65-4-4-H3-FL1	333	DNA	
74-3-1-B9-FL1	334	DNA	
76-4-1-G5-FL1	335	DNA	
76-7-3-A12-FL1	336	DNA	
76-16-4-C9-FL3	337	DNA	
76-30-3-B7-FL1	338	DNA	
77-5-1-C2-FL1	339	DNA	
77-5-4-E7-FL1	340	DNA	
77-11-1-A3-FL1	341	DNA	
77-16-3-D7-FL1	342	DNA .	
77-16-4-G3-FL1	343	DNA	
77-25-1-A6-FL1	344	DNA	
77-26-2-FL3	345	DNA	
78-6-2-E3-FL2	346	DNA	
78-7-1-G5-FL2	347	DNA	
78-16-2-C2-FL1	348	DNA	
78-18-3-B4-FL3	349	DNA	
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78-29-1-B2-FL1	358	DNA	
78-29-4-B6-FL1	359	DNA	
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30-9-1-G8-FL2	361	DNA	
33-10-4-H2-FL2	362	DNA	
33-10-4-H2-FL1	363	DNA	
74-10-3-C9-FL2	364	DNA	
33-97-4-G8-FL3	365	DNA	
33-97-4-G8-FL2	366	DNA	
33-104-4-H4-FL1	367	DNA	
47-2-3-B3-FL1	368	DNA	
47-37-4-G11-FL1	369	DNA	

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370 371 372 373 374 375 376 377 378 379 380 381 382 383	DNA
372 373 374 375 376 377 378 379 380 381	DNA DNA DNA DNA DNA DNA DNA PRT PRT PRT PRT
373 374 375 376 377 378 379 380 381	DNA DNA DNA DNA DNA DNA PRT PRT PRT PRT PRT
374 375 376 377 378 379 380 381 382	DNA DNA DNA DNA PRT PRT PRT PRT PRT
375 376 377 378 379 380 381 382	DNA DNA DNA PRT PRT PRT PRT PRT
376 377 378 379 380 381 382	DNA DNA PRT PRT PRT PRT PRT
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384	PRT
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100	PRT
101	PRT
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03	PRT
04	PRT
05	PRT
06	PRT
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33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
48-4-2-H3-FL1	416	PRT
48-6-1-C9-FL1	417	PRY
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	425	PRT
48-29-1-E2-FL1	426	PRT
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
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51-2-3-F10-FL1	433	PRT
51-2-4-F5-FL1	434	PRT
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	PRT
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51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	PRT

51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
58-26-3-D1-FL1	452	PRT
57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
59-9-4-A10-FL1	465	PRT
60-16-3-A6-FL1	466	PRT
60-17-3-G8-FL2	467	PRT
62-5-4-B10-FL1	468	PRT
65-4-4-H3-FL1	469	PRT
74-3-1-B9-FL1	470	PRT
76-4-1-G5-FL1	471	PRT
76-7-3-A12-FL1	472	PRT
76-16-4-C9-FL3	473	PRT
76-30-3-B7-FL1	474	PRT
77-5-1- <b>C2</b> -FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT

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78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-B6-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-B3-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3- <b>C9-F</b> L2	508	PRT
58-48-4-E2-FL2	509	PRT
76-21-1-C4-FL1	510	PRT
78-26-2-H7-FL1	511	PRT
77-20-2-E11-FL1	512	PRT
47-1-3-F7-FL2	513	PRT

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## TABLE VIII

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10-34	Protein kinases ATP-binding region signature

### WHAT IS CLAIMED IS:

- 1. A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
  - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID Nos: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48,
   49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- 5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.
  - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
- A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
    - A purified or isolated protein comprising the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
  - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

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obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

- The method of Claim 13, further comprising the step of isolating said protein.
  - 15. A protein obtainable by the method of Claim 14.

cDNA.

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- 16. A host cell containing a recombinant nucleic acid of Claim 1.
- 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- 19. A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent
   15 conditions to the sequence of one of SEO ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEO ID NOs: 40-140 and 242-377.
  - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

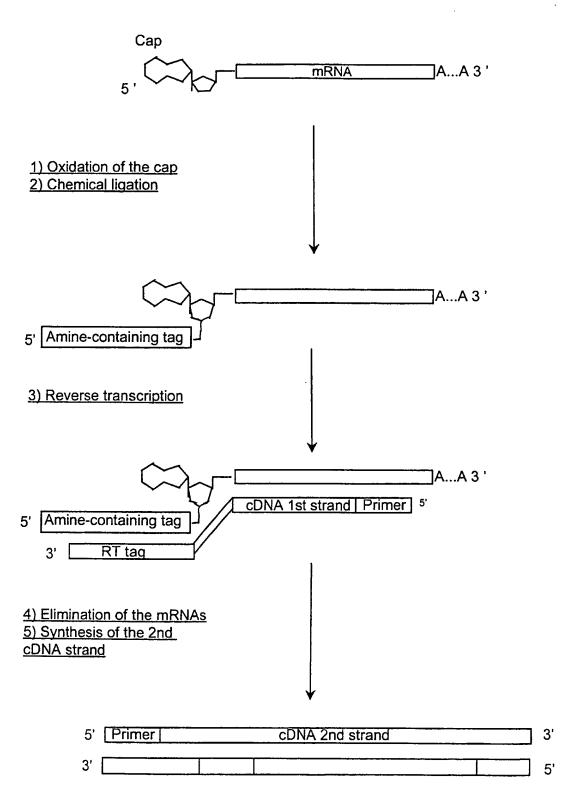
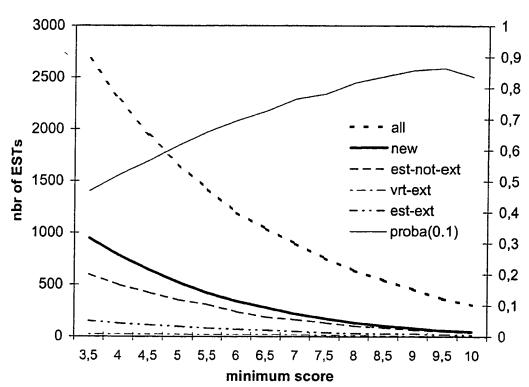


Figure 1

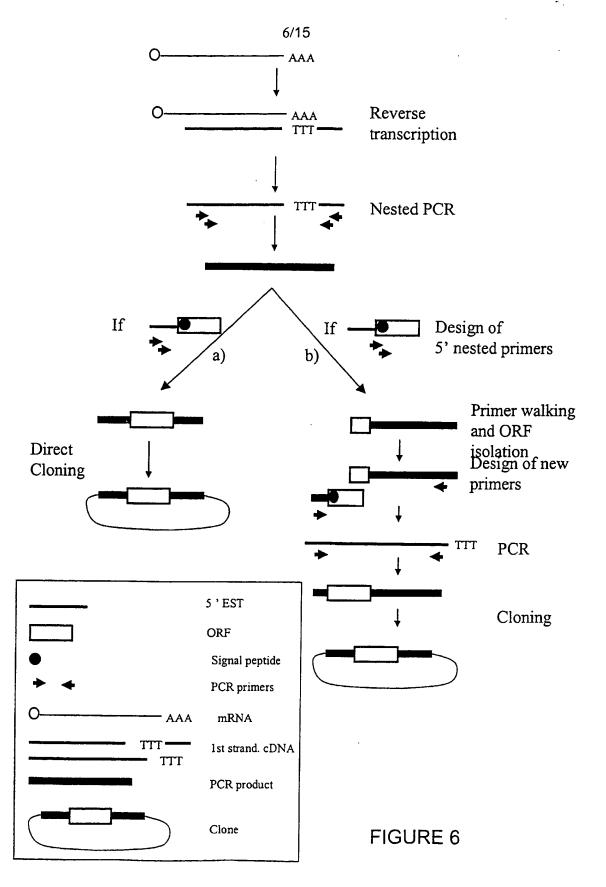
Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

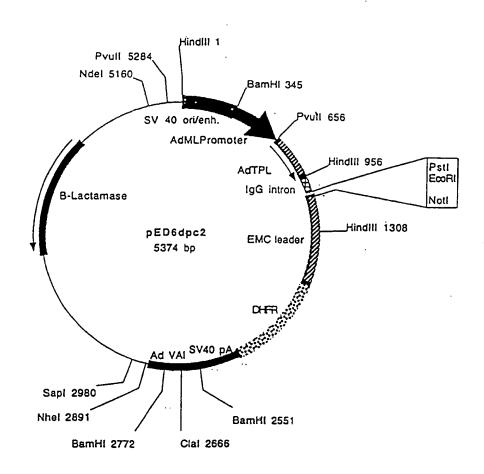
# influence of minimum score on signal peptide recognition



Minimum signal peptide score		New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

	<del></del>				
Tissue	`All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	0	6
Colon	21	11	4	0	Ö
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	Ō	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	Ö	0
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	õ
Large intestine	21	8	4	0	1
Liver	23	9	6	0	o
Lung	24	12	4	Ō	1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	0
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	o
Testis	131	68	25	1	8
Thyroid	17	8	2	0	2
Umbilical cord	55	17	12	1	2 3
Uterus	28	15	3	0	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150





Plasmid name: pED6dpc2 Plasmid size: 5374 bp 8/15

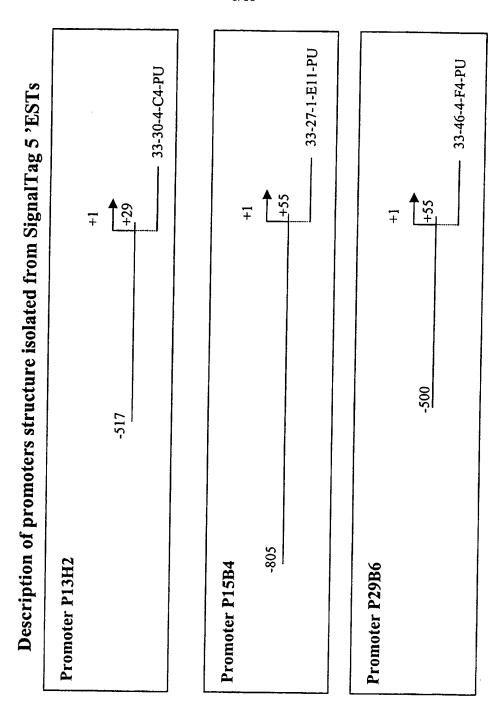


FIGURE 8

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# Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

## Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	◄.	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	-	0.960	11	GCACACCTCAG
GATA_C	-364	•	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	•	0.954	10	ACCATCTGTT
GATA1_04	-217	•	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41		0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

## Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	•	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

## Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

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100.0% identity in 125 aa overlap 20 30 40 50 SEQ ID NO: 217 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA 10 20 30 40 50 60 70 80 90 100 110 120 SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD 70 80 90 100 110 SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

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FIGURE 10

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CLUSTAL W(1.5) multiple sequence alignment

SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 174	LKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKCIFKIDWTLSMGCVFQSTEDKRIFKIDWTLSMGCVFQSTVDKCIFKIDWTLS ******* ** ********
SEQ ID NO: SEQ ID NO: SEQ ID NO: SEQ ID NO:	232 PGEH 174 PGEH 175 PGEH	AKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVEAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL AKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQEADQGTYICEIRL AKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
SEQ ID NO:	232 KGES 174 KGES	QVFKKAVVLHVLPEEPKGTQMLTQVFKKAVVLHVLPEEPKGLMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE
SEQ ID NO:	232 174 IVFR	YYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN KHHCVREGSG
SEQ ID NO: 5 SEQ ID NO: 5 SEQ ID NO: 5 SEQ ID NO: 5	232 174 LVFK	KTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ ID NO: 5 SEQ ID NO: 3 SEQ ID NO: 1	232 174 GNKS	SVNSTVLVKNTKKTNP

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99.6% identity in 225 aa overlap SEQ ID NO: 515 PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 231 LRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 515 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 231 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 515 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 231 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 515 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 231 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 515 HFPNEFIVETKICQE 

SEQ ID NO: 231 HFPNEFIVETKICQE

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99.7% identity in 353 aa overlap SEQ ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY \* SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL 

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98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN ............. SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL SEQ ID NO:519 AS

SEQ ID NO:158 PP

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68.9% identity in 74 aa overlap

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SEQ ID NO:514 MMTGRQGRATFQFLPDEARSLPPPKLTDPRLAFVGFLGYCSGLIDNAIRRRPVLLAGLHR

20 30 40 50 60

60 70

SEQ ID NO:226 QLLYITAFFLLDIIL

SEQ ID NO:514 QLLYITSFVFVGYYLLKRQDYMYAVRDHDMFSYIKSHPEDFPEKDKKTYGEVFEEFHPVR 70 80 90 100 110 120

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125 130	135
tgc atc atc ata gtt gca att gca cta ctg att tta t	
Cys Ile Ile Ile Val Ala Ile Ala Leu Leu Ile Leu S	-
	50 at gac gct gaa 580
caa cgt ada ara aag aac aaa gaa cca tct gaa gtg g	
Gln Arg Xaa Xaa Lys Asn Lys Glu Pro Ser Glu Val A 155 160 165	sp Asp Ala Giu
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Xaa Xaa Cys Glu Asn Met Ile Thr Ile Glu Asn Gly I	<b>-</b>
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gca	tacc	tga	tccc	caqt	tc c	tata	ccct	a cc	cctq	acct	att	gago	agc	ctct	gaagag	1313
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170

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Thr	Tvr	Asn	Lvs	His	Ile	Asn	Ile	Ser	Phe	His	Arg	Phe	Pro	Leu	Asp	
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cct	aaa	aga	aga	aaa	gaa	tgg	gtt	cgc	ctg	gtt	agg	cgc	aaa	aat	ttt	266
Pro	Lys	Arg	Arg	Lys	Glu	Trp	Val	Arg	Leu	Val	Arg	Arg	Lys	Asn	Phe	
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Cys	Phe	Asp	Leu		Gly	Gln	Thr	Arg		Leu	Lys	Met	Asp		Val	
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ser	Arg		Leu	Leu	Lys	гÀг		ASII	Ser	Cys	ser	105	AIA	GLY	PIO	
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Cor	agt	Ton	Tuc	Cox	Asn	Tla	cor	car	Gln	Gln	Val	Len	Len	Glu	His	300
ser	110	ьеи	гур	Sei	ASII	115	Ser	261	GIII	GIII	120	Deu	Бец	GIU	1115	
200		~~~	+++	200	aat		ato	man.	aca	222		agg	atc	att	aaa	554
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	ma a	222	na a	ata	gca	age	tta	ада	aga		ato	aaa	act	tac		602
Len	Glu	Lve	Glu	Tle	Ala	Ser	Len	Ara	Ara	Lvs	Met	Lvs	Thr	Cvs	Leu	
neu	010	Dy U	0.14	145				5	150	-1-		-1-		155		
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Gln	Lvs	Glu	Ara	Ara	Ala	Thr	Arg	Arg	Tro	Ile	Lvs	Ala	Met	Cys	Leu	
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Val	Lys	Asn	Leu	Glu	Ala	Asn	Ser	Val	Leu	Pro	Lys	Gly	Thr	Ser	Glu	
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cac	atg	tta	cca	act	gcc	tta	agc	agt	ctt	cct	ttg	gaa	gat	ttt	aag	746
His	Met	Leu	Pro	Thr	Ala	Leu	Ser	Ser	Leu	Pro	Leu	Glu	Asp	Phe	Lys	
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Lys	Gln	Thr	Lys		Thr	Phe	Ile									
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															agaata	968
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WO 99/31236 -38- PCT/IB98/02122 .

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682

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tgc cca aat tta aag gaa gtt tgt ctc att ttg cca gaa aaa aat tgt Cys Pro Asn Leu Lys Glu Val Cys Leu Ile Leu Pro Glu Lys Asn Cys 40 45 50	245
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Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala Glu
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                       -35
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Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His His
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                    -20
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Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala
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Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro Cys
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Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His Asn
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                                        50
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Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu Glu
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Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg Lys
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ata gta gaa gct tgt aaa gcc aaa act gat gct ggc ggt gaa gat gct
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Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg Gln	
155 160 165	
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Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His Val	
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aag aaa aca gtg acc att gaa aat cat cct cat ctg cca cca cct ccc	024
Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro	
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transporter appropriate aggregate aggregate aggregate aggregate aggregate	360
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tgecegegtg teagacteea teecteetet geegecaceg cageagecae aggtag atg	_

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Arg Thr Arg Thr Thr Gly Asn Pro Arg Gly Leu His Asp Thr Phe Pro -75 -70 -65	
cgc aga ccc aga ctt ggc cgt tgc tct gac atg gac aca gcc agg aca Arg Arg Pro Arg Leu Gly Arg Cys Ser Asp Met Asp Thr Ala Arg Thr	755
-60 -55 -50	
age tge tea gae etg ett eee tgg gag ggg gtg acg gaa eea gea etg	803
Ser Cys Ser Asp Leu Leu Pro Trp Glu Gly Val Thr Glu Pro Ala Leu -45 -40 -35	
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Cys Gly Asp Gln Leu Gln Gly Thr Glu Gly Trp Leu Glu Ala Thr Gln	
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Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly Ser	
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1 5 10 atg aag agt cgg gag cag gga gga cgg ctg gga gcc gaa agc cgg acc	146
Met Lys Ser Arg Glu Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr	
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30 35 40	
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Thr Val Leu Gly Leu Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys 45 50 55 60	
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Phe Ser Ala Val Phe Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu 65 70 75	
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Asn Val Ser Gly Glu Phe Gly Trp Ser Phe Cys Leu A	la Cys val Ser
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Lys Leu Phe Asp Ala Pro Leu Ser Ile Ser Lys Arg Glu Gln Leu Glu
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Pro Glu Ile Asp Val Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala
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aat aag aaa ggc aac gtt ttg cag ctt cca aat ttc tgaagaaact Asn Lys Lys Gly Asn Val Leu Gln Leu Pro Asn Phe 25 30	195
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	gly ggg		cct					tta					gta			201
	ctg Leu	aac				aag					ttc					249
gca	ggc	ccc Pro	ctg Leu	gca Ala 35	gtg Val	gcc Ala	gct Ala	gtg Val	cta Leu 40	tat Tyr	cat His	aag Lys	atg Met	aac Asn 45	aat Asn	297
	aag Lys			gaa												345
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Ile atc	tat Tyr 80	gct														
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Tyr Glu	ı Trp	Tyr	Gln	Glu	Tyr	Tyr	Val	Gly	Ala	Ala	His	Gly	Leu	Ala	
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Gly Ile		Tyr	Tyr	Leu	Met		Pro	Ser	Leu	Gln		Ser	GIn	GIÀ	
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Lys Let		Ser	ьeu	vaı		Pro	ser	vaı	Asp	171 170	vaı	Сув	GIII	neu	
160 aaa tt		+	~~~	+	165	cct	cca	tat	ata		cat	aat	cga	gat	729
Lys Ph	a Dro	Car	Glv	Acn	Tur	Dro	Dro	CAC	Tle	Glv	Asp	Asn	Ara	Asp	
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ctg ct	t atc	cat	taa		cat	aac	acc	cct		gta	atc	tac	atq		777
Leu Le	ı Val	His	Trp	Cvs	His	Glv	Ala	Pro	Gly	Val	Ile	Tyr	Met	Leu	
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Tyr Gl		Cys	His	Gly		Ala	Gly	Asn	Ala		Ala	Phe	Leu	Thr	
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Phe Al	a GIu	Trp	275	neu	Gru	ıyı	Gīy	280	птв	Gry	Cys	nr 9	285	110	
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Pob III		290	001				295			2		300	•		
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Leu															
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gggaga	gtga	gtga	tatg	ta c	agtg	tttt	g ag	attg	tata	cat	atat	tcc .	agaa	cttgga	1406
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gaa aaa cac aca cac aca cac aca cat ata cac aca cac ac Glu Lys His Thr His Thr His Thr His Ile His Thr His Th	a cga aaa 401 ar Arg Lys 25
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ggc tac gca gca ctg gtt gct tct ggt ggg atc att ggc t Gly Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly T	at gta aaa 155
gca ggc agc gtg ccg tcc ctg gct gca ggg ctg ctc ttt gg Ala Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe G	gc agt cta 203
gcc ggc ctg ggt gct tac cag ctg tct cag gat cca agg a Ala Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg A 1 5 10	ac gtt tgg 251 sn Val Trp 15
gtt ttc cta gct aca tct ggt acc ttg gct ggc att atg g Val Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met G 20 25	ga atg agg 299 ly Met Arg 30
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tgc cag cgt cgc tgg cct gac cgc cgc tgc cta cag agt cac act caa Cys Gln Arg Arg Trp Pro Asp Arg Arg Cys Leu Gln Ser His Thr Gln 35 40 45	145
tcc tcc ggg cac ctt cct nntgaaggag tggctaaggt tggacaatac Ser Ser Gly His Leu Pro 50	193
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gactetggga geacgeacge acaactacgg gattggegee geegeetgeg tgtactttgg	373
catagoggco tocotggtca agatgggcog gotggagggc tgggaggtgt ttgcaaaaco	433
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gcg gca gtg gcg cct gtc ctg tcc ata aac agc gat ttc tca gat ttg	9
Ala Ala Val Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu -5 5 5	
cgg gaa att aaa aag caa ctg ctg ctt att gcg ggc ctt acc cgg gag Arg Glu Ile Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu 10 15 20	14
con one of the car and are as ton ten ord day the art the tet	19

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Arg 25	Gly	Leu	Leu	His	Ser 30	Ser	Lys	Trp	Ser	Ala 35	Glu	Leu	Ala	Phe	Ser 40	
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Phe	Asp	Val 75	Lys	Glu	Tyr	Asp	Arg 80	Ala	Ala	His	Phe	Leu 85	His	Gly	Cys	
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	90					95					100			Leu		
agg	gcc	att	tta	aaa	tgt	cat	tct	gcc	ttt	agt	gaa	aca	tcc	ata	ttt	435
Arg	Ala	Ile	Leu	Lys	Cys	His	Ser	Ala	Phe	Ser	Glu	Thr	Ser	Ile		
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aga	acc	aat	gga	aaa	gtt	aaa	tct	ttt	aaa	tage	ttaç	gca g	gtgg	gccad	et	485
Arg	Thr	Asn	Gly	Lys	Val	Lys	Ser	Phe	Lys							
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	TIG	TIII	val	-10	nea	±€.ft	1.16.0	Tie a	-5	* G T	1111	uu		1		
				tcc					aac					aac Asn		148

atc	ttc	gag	aac	ctc	tgg	ttt	agc	tgt	gcc	acc	gac	tcc	ctg	ggc	gtc	196
Ile		Glu	Asn	Leu	Trp		Ser	Cys	Ala	Thr		Ser	Leu	Gly	Val	
	20		+~~	~~~	++0	25	+ = =	ato	cta	acc	30 ct c	tct	aaa	tat	att	244
Tur	aac Aen	Cvs	Trn	Glu	Phe	Pro	Ser	Met	Leu	Ala	Leu	Ser	Glv	Tyr	Ile	
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Gln	Ala	Cys	Arg		Leu	Met	Ile	Thr		Ile	Leu	Leu	Gly	Phe	Leu	
			a+ >	55	252	~~~	<i>aac</i>	cta	60	tac	200	220	att	999 65	aac	340
ggc	Len	Len	Leu	Glv	Ile	Ala	Glv	Leu	Ara	Cvs	Thr	Asn	Ile	Gly	Gly	• • • •
Ory	200		70	1			1	75	5	-2-			80	•	•	
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uie	Tle	T.Au	gee	Glv	Tle	Cvs	999 61v	Met	Val	Ala	Tle	Ser	Tro	tac Tyr	Ala	130
nrs	100	пец	AIU	Oly	110	105	O-7				110	001		-1-		
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	180					185					190					
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gaa ata ata tcc ttg aaa gag gaa tca cca tta gga aag gtg agt cag Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly Lys Val Ser Gln -40 -35 -30	162
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Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser 1 5 10 15  ttg ccc cat ggt gtc ctg gga ccc aga gca aca gga tct gtc acc cac Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His 20 25 30  ctc tct ctt ctc ccc cag atc aag caa cgt gcc tca gag gct ttg ccc Leu Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro 35 40 45  gaa ttg ctt cgt cct gtc acc ccc atc acc aat ttt gag ggc agc cag Glu Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln 50  tct cag gac cac agt gga atc ttt ggc ctg gta aca aca ctg gaa gag Ser Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Glu 65 70 75  ctg gag gtg gac gat tgg gag ttc tgagcetctg caaactgtgc gcattetcca Leu Glu Val Asp Asp Trp Glu Phe 80 85  gccagggatg cagaggccac ccagaggccc ttcctgaggg ccggccacat tcccgccctc ctgggcagat tgggtagaaa ggacattett ccaggaaagt tgactgctgg ctgattgga aagaaaatcc tggagagata ctcactgct ccaaagcett tgagacacaa gggaatctca accaccaggg atcagaggg ctccaaagccg acatteccag tcctccgcag aagagagg ctccaaagccg acatteccag tcctcgagag tccaaagcag cccacctet tcccaggagac ttccagaggac ctcctcaactct tcccaggagac gaatccaa cccagggttt ggctccttaa acccagaggc ctccagatgct ttcccagagc ttcctcacctca	110 158 206 254 302 356 416 476 536 596 656 716 776 836
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Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser 1 5 10 15  ttg ccc cat ggt gtc ctg gga ccc aga gca aca gga tct gtc acc cac Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His 20 25 30  ctc tct ctt ctc ccc cag atc aag caa cgt gcc tca gag gct ttg ccc Leu Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro 35 40 45  gaa ttg ctt cgt cct gtc acc ccc atc acc aat ttt gag ggc agc cag Glu Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln 50  tct cag gac cac agt gga atc ttt ggc ctg gta aca acc ctg gaa gag Ser Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu 65 70 75  ctg gag gtg gac gat tgg gag ttc tgagcctctg caaactgtgc gcattctcca Leu Glu Val Asp Asp Trp Glu Phe 80 85  gccagggatg cagaggccac ccagaggcc ttcctgagg ccggccacat tcccgcctc ctggcagat tgggtagaaa ggacattct ccaggaagt tgagagaggag tccaaagccg acattctc ccaggaagat tgggtagaaa ggacattct ccaggaagt tgagagaggg tccaaagccg acattccca tcccgcaga atcaccaggg tccaaagccg acattccca acaccaggg atcaggagat ctccaaagccg acattccca tccaggagct tccaaagcg accaccactct tccaggaagt gaatccaa accacagga tccaaagcg cccacctct tccaggagct gaattccaag cccagggttt ggctcctaa acccaggac ctcaatccc ctacagtgct tgcgaccagc ctcattctac ttaactttg tctcagatgc ctcagatgct ataggtcag gaaaggcag ttcctctac accaccac gaccaccac acctccc ctacattcca gacaaagcca ttctcttac tttaactttg tctcagatgc ctcagatgct ataggtcag gaaaggca ttctctcttttac tttaacctca gaccaagcc ctctctccac gaccaccaccaccaccaccaccaccaccaccaccaccacc	110 158 206 254 302 356 416 476 536 596 656 716 776 836 896 956

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Tyr Asn Arg Val Pro Leu His Lys Pro Thr Asp Trp Gln Lys Lys Ile 55 60 65 70	
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Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu Asp Glu Ile Pro Glu Thr 75 80 85	
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Val Ser Leu Glu Met Leu Asp Ala Ala Lys Asn Lys Met Arg Val Lys 90 95 100	
age age tat eta atg att gee etg acg gtg gta gga tge ate tte atg	389
Ser Ser Tyr Leu Met Ile Ala Leu Thr Val Val Gly Cys Ile Phe Met 105 110 115	
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Val Ile Glu Gly Lys Lys Ala Ala Gln Arg His Glu Thr Leu Thr Ser 120 125 130	
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Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys Glu Glu Ala Ala Met Lys	
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Phe	Gln	Glu 250	Asp	Pro	Glu	Ala	Phe 255	Leu	Leu	Tyr	His	Arg 260	Gly	Phe	Gln	
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														Ala		
gat		cac	cag	caa	cct		tac	cta	ata	ata		gac	ttc	ggc	tat	1021
														Gly		
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ggg	gat	tgc	cgc	ttg	gct	tca	agt	atc	cgg	aac	CCT	gtg	cat	tgc	בבב	1069
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Asp	Leu	Ala	Ser 315	Leu	Asp	Pro	Arg	Val 320	Thr	Val	Суş	Asp	Met 325	Ala	Gln	
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Val	Pro	Leu 330	Glu	Asp	Glu	Ser	Val 335	Asp	Val	Ala	Val	Phe 340	Cys	Leu	Ser	
ctq	atq	qqa	acc	aac	atc	agg	gac	ttc	cta	gag	gag	qca	aat	aga	gta	1213
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Leu	Lvs	Pro	Glv	Glv	Leu	Leu	Lvs	Val	Ala	Glu	Val	Ser	Ser	Arg	Phe	
360	-1-		1	1	365					370					375	
	cat	att	caa	acc		cta	caa	act	ata		aag	cta	aac	ttc	aaq	1309
														Phe		
2++	ata	+	224		a+ a	200	220	200		++0	ttc	tta	+++	gat	ttc	1357
																133,
			395	_				400					405	Asp		
														tca		1405
	_	410	_				415					420		Ser		
ctg	cag	ctt	cag	cca	tgt	ctc	tac	aag	cgc	agg	tga	cctc	tgg	atct	t <b>cctt</b> g	1458
			Gln													
aga		agg (	cagai	tata	aa a		agge	t ca	gaact	tata	aao	acto	ttt	ccaa	cctggc	1518
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1678

243

291

338

398

458

494

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ttc acg gaa cct aat gaa ata tcc cag tat tta cca ata aag gaa gca Phe Thr Glu Pro Asn Glu Ile Ser Gln Tyr Leu Pro Ile Lys Glu Ala

gtt tgt gag aag cta ata ttt cca gaa aga att gat cct aac cca gca

Val Cys Glu Lys Leu Ile Phe Pro Glu Arg Ile Asp Pro Asn Pro Ala
60 65 70

actcactatg gaatctgact ggacaccttg gctatttgta aggggttatt tttattatga

gaattaattg ccttgtttat gtacagattt tctgtagcct taaaggaaaa aaaaataaag

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gct gct ttc tcc gtc ctc ccc tgt tac tac ctt ggg ctg ttt cag cgg Ala Ala Phe Ser Val Leu Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg -15 -10 -5	161
gcg ctc gcg tcg gtc ttc gac cca ctt tgc gtt tgt tca cgt gtg ctc Ala Leu Ala Ser Val Phe Asp Pro Leu Cys Val Cys Ser Arg Val Leu 1 5	209
ccg aca cct gta tgt acc ttg gtc gca aca caa gcc gaa aaa ata tta Pro Thr Pro Val Cys Thr Leu Val Ala Thr Gln Ala Glu Lys Ile Leu 15 20 25	257
gag aat ggg ccc tgt cca acc aag gag gcg gcc cag ctt gtc ggg aag Glu Asn Gly Pro Cys Pro Thr Lys Glu Ala Ala Gln Leu Val Gly Lys 30 35 40 45	305
ggc agc gtt tcc gcc aga aat gct tcg tgaaaggcac ttgagggacc Gly Ser Val Ser Ala Arg Asn Ala Ser	352
ttagcagcat cctcaacagg ccttgtaggg aatgccagaa gaagcagtcc ttggccgggc gggtggctc atgcctgtgg tcccagcact ttgggaggcc ggggcgggcg gatcacctga ggtcgggagg tccagaccag cctgaccgac atggagaaac cccgtctnta ctagaaatac aaaactagcc gggtgtggtg gcgcatgcct gtagtcccag ctactcggga gggtgaggca ggagacgttc ttgaacccgg gaggcggagt ttgtggtgag ccgagatcgc gccattgcac tccagcctgg gcatgccaag agcgaaactc cgtctcaaaa aaaaaaaaaa	412 472 532 592 652 712 714
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ggg gcg gcc ggc ttc aca cct tcc ctc gat agc gac ttc acc ttt acc Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe Thr 1 10 15	148
ctt ccc gcc ggc cag aag gag tgc ttc tac cag ccc atg ccc ctg aag Leu Pro Ala Gly Gln Lys Glu Cys Phe Tyr Gln Pro Met Pro Leu Lys 20 25 30	196
gcc tcg ctg gag atc gag tac caa gtt tta gat gga gca gga tta gat Ala Ser Leu Glu Ile Glu Tyr Gln Val Leu Asp Gly Ala Gly Leu Asp 35 40 45	244
att gat ttc cat ctt gcc tct cca gaa ggc aaa acc tta gtt ttt gaa Ile Asp Phe His Leu Ala Ser Pro Glu Gly Lys Thr Leu Val Phe Glu	292
caa aga aaa tca gat gga gtt cac act gta gag act gaa gtt ggt gat Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly Asp	340
tac atg ttc tgc ttt gac aat aca ttc agc acc att tct gag aag gtg Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val	388
att ttc ttt gaa tta atc ctg gat aat atg gga gaa cag gca caa gaa Ile Phe Phe Glu Leu Ile Leu Asp Asn Met Gly Glu Gln Ala Gln Glu	436
caa gaa gat tgg aag aaa tat att act ggc aca gat ata ttg gat atg Gln Glu Asp Trp Lys Lys Tyr Ile Thr Gly Thr Asp Ile Leu Asp Met	484
aaa ctg gaa gac atc ctg gaa tcc atc agc agc atc aag tcc aga cta Lys Leu Glu Asp Ile Leu Glu Ser Ile Ser Ser Ile Lys Ser Arg Leu	532
agc aaa agt ggg cac ata caa att ctg ctt aga gca ttt gaa gct cgt Ser Lys Ser Gly His Ile Gln Ile Leu Leu Arg Ala Phe Glu Ala Arg 145 150 150 160	580
gat cga aac ata caa gaa agc aac ttt gat aga gtc aat ttc tgg tct Asp Arg Asn Ile Gln Glu Ser Asn Phe Asp Arg Val Asn Phe Trp Ser 165 170 175	628
atg gtt aat tta gtg gtc atg gtg gtg gtg tca gcc att caa gtt tat  Met Val Asn Leu Val Val Met Val Val Ser Ala Ile Gln Val Tyr  180 185 190	676
atg ctg aag agt ctg ttt gaa gat aag agg aaa agt aga act Met Leu Lys Ser Leu Phe Glu Asp Lys Arg Lys Ser Arg Thr 195 200 205	718
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<222> 26..88

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Ile Glu Leu Phe Gly Leu Glu Asn Asp Phe Ser Gln Glu Ser Ser

120
125
130

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tcttttatct gttttggatt cactgtgctt ttaagaaaaa gttggtaaat ttgccgttga 721
ttttctttt taacctcaaa ctaatagaat tttataaaat attaatttc tccaaaaaaa 781
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481

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tot tog cog tot ttg aaa aca	ana:nan taa		act gca 100
Ser Ser Pro Ser Leu Lys Thr	den The Ser	Pro Val Leu Glu	Thr Ala
-45 -40	ASP III SEL	-35	-30
gga acg gtc gca gca atg gct	aca acc cca		gca gcc 148
Gly Thr Val Ala Ala Met Ala	Ala Thr Pro	Ser Ala Arg Ala	Ala Ala
-25	-20		-15
gcg gtg gtt gcg gcc gcg gcc	agg acc gga	tcc gaa gcc agg	gtc tcc 196
Ala Val Val Ala Ala Ala Ala			
-10	-5	1	
aag gcc gct ttg gct acc aag			
Lys Ala Ala Leu Ala Thr Lys	Leu Leu Ser	Leu Ser Gly Val	Phe Ala
5 10		15	
gtg cac aag ccc aaa ggg ccc	act tca gcc	gag ctg ctg aat	cgg ttg 292
Val His Lys Pro Lys Gly Pro	Thr Ser Ala		
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40	45	est ags agg sat	<del>-</del> -
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age gea gee ega gga gtt etg			aca aaa 436
Ser Ala Ala Arg Gly Val Leu			
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Met Leu Thr Ser Met Leu Ser			
85 90		95	
gaa ctg ggg aaa gct act gat	aca cta gat	tct acg ggg aag	gta aca 532
Glu Leu Gly Lys Ala Thr Asp	Thr Leu Asp	Ser Thr Gly Lys	Val Thr
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score 6.8
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ctg	CLL	gaa	gag	CEE	Dwo	Tou	Dro	yac Nen	Cay	Gln	Dro	Cvs	Ile	Glu	Pro	
ьeu	Leu	-75	GIU	neu	PIO	пец	-70	Yob	0111	01	110	-65				
			+	250	2+4	tac		act	aac	+++	gac		aac	ttt	gag	144
Dro	Dro	Car	Ser	Tla	Met	Tur	Gln	Δla	Asn	Phe	Asp	Thr	Asn	Phe	Glu	
PIO	-60	Sel	Ser	116	Mec	-55	<b>Q1</b> 11	AIG	11011		-50					
aac.		aat	aca	+++	atc		aac	att	gca	agg		att	gag	caq	gct	192
) ac	Ara	Aar	Mla	Phe	Val	Thr	Glv	Ile	Ala	Ara	Tvr	Ile	Glu	Gln	Ala	
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Thr	Val	Hig	Ser	Ser	Met	Asn	Glu	Met	Leu	Glu	Glu	Gly	His	Glu	Tyr	
+111 ,	vul			-25					-20			•		-15	<del>.</del>	
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yla gcg	Val	Met	Len	Tvr	Thr	Trn	Ara	Ser	Cvs	Ser	Arg	Ala	Ile	Pro	Gln	
AIG	vaı	Mec	-10	- 7 -	1111	1.5		-5	-,-		3		1			
ata	222	tac		gag	cad	ccc	aac		σta	gag	atc	tat	gag	aaq	aca	336
ycy Val	Lvc	Cyc	Aen	323	Cln	Pro	Asn	Ara	Val	Glu	Ile	Tvr	Glu	Lvs	Thr	
Val	БуБ 5	Cys	ASII	014	0111	10					15	-1		<b>2</b> .		
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yca val	Glu	77-1	Len	Glu	Dro	Glu	Val	Thr	Lvs	Len	Met	Lvs	Phe	Met	Tvr	
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Dhe	Gln	Ara	Larg	Δla	Tle	Glu	Ara	Phe	Cvs	Ser	Glu	Val	Lys	Arq	Leu	
FIIC	GIII	тà	Буз	40	110	0	9		45				-1-	50		
tac	cat	acc	asa		agg	aaq	gac	ttt		tct	gag	acc	tac	ctc	ctg	480
Cyc	Tie.	Δla	Glu	Ara	Ara	Lvs	Asp	Phe	Val	Ser	Glu	Ala	Tyr	Leu	Leu	
Cys	1110	nıu	55	9	3	-1-	····	60					65			
acc	ctt	aac		ttc	atc	aac	ato		act	atc	ctq	qat	gag	cta	aag	528
Thr	Len	Glv	Lvs	Phe	Tle	Asn	Met	Phe	Ala	Val	Leu	Asp	Glu	Leu	Lys	
1111	Deu	70	ט עַם	1110		***	75					80			-	
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Acn	Met	I.ve	Cve	Ser	Val	Lvs	Asn	Asp	His	Ser	Ala	Tvr	Lys	Arg	Ala	
Aon	85	275	Cys			90					95	1	•	•		
aca		ttc	cta	caa	aaq		aca	gat	ccc	caq	tct	atc	cag	gag	tcg	624
Δla	Gln	Phe	Len	Ara	Lvs	Met	Ala	Asp	Pro	Gln	Ser	Ile	Gln	Glu	Ser	
100	0111	1110	<u> L</u> Cu	*** 9	105					110					115	
	aac	ctt	tcc	ato		cta	acc	aac	cac			atc	acc	cag	tgt	672
Cln	Aen	Len	Ser	Met	Phe	Leu	Ala	Asn	His	Asn	Arq	Ile	Thr	Gln	Cys	
GIII	YOU	пси	Jer	120	1110	200								130		
ctc	cac	cac	caa		gaa	ata						gag	ctg	ctq	qct	720
Leu	Hig	Gln	Gln	Len	Glu	Val	Tle	Pro	Glv	Tvr	Glu	Glu	Leu	Leu	Āla	
DCu	1113	0111	135		014			140		-1-			145			
asc	att	ate			tat	ata	gat			gag	aac	aad			ctg	768
) cn	Tle	7721	Acn	Tle	Cyc	Val	Asn	Tyr	Tvr	Glu	Asn	Ivs	Met	Tvr	Leu	
veh	110	150	A511	110	Cys	• • • •	155		-1-		0-200	160		- 3		
act	~~~		asa	222	cat	ato			aad	gta	aaa		ccc			810
The	Dec	ayı Ser	gay	Tare	His	Mo+	T.e.11	Len	Lve	Val	Lve	Len	Pro	,		
THE			GIU	пÀг	птв	170		cu	y 5	+ 111	175					
<b>+</b>	165			+ ~~-	aa -			c cc	tete	acc+			att	aaaa	atccgt	870
							CLLA			الالالا				~~u		893
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cac gtg aag atg ctg cgg ctg gtg ttt gca ctt gtg aca gca gta tgc His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr Ala Val Cys -15 -10 -5	152
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ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca gaa Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu 20 25 30 35	291
caa ggt tta ata gaa atc ctt aaa aaa gta agc caa caa aca gaa aag Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Lys 40 45 50	339
aca aca aca gtg aaa ttc aac aga aga aaa gta atg gac tct gat gaa Thr Thr Thr Val Lys Phe Asn Arg Arg Lys Val Met Asp Ser Asp Glu 55 60 65	387
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•	•															
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gca Ala	ctg Leu	ctt Leu	cgc Arg	30 ctc Leu	ctg Leu	ccg Pro	gag Glu	Tyr	35 cgg Arg	gat Asp	gca Ala	gag Glu	Ile	gtg	cgg Arg	243
acc Thr	cgg Arg	gat Asp	45 ccc Pro	gaa Glu	aaa Lys	ctc Leu	gct Ala	50 tcc Ser	tgt Cys	gac Asp	atc Ile	gtg Val	55 gtg Val	gac Asp	gtg Val	291
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tct Ser	75 ttc Phe	aca Thr	gag Glu	acc Thr	atg Met	80 agc Ser	tcc Ser	ctg Leu	tcc Ser	cct Pro	85 999 Gly	agg Arg	ccg Pro	tgg Trp	Gln	387
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Ile	Gln	Сув	Val 285	Pro	Lys	Glu	Pro	His 290	Ser	Phe	Gln	Ser	Arg 295	Leu	Pro	1011
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Ser	Gly 315	7 Il∈	Pro	Gly	r Cys	320	Phe	e Val	His	Ala	Ser 325	Gly	Phe	: Ile	ggc	
Gly 330	His	Arg	y Thr	Arg	335 335	Gly	Ala	a Leu	Ser	Met 340	: Ala	a Arg	, Ala	t Thr	Leu 345	1107
gcc Ala	Glr	Arg	tca Sei	tac Tyr	c cto	cca Pro	caa Glr	a ato 1 Ile	tco Ser	tag	gtcta	aata	aaac	ctto	ca	1157

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150

tee cae tee agg etg tee eec ega aag ace cae tta etg tae ate etc

686

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Gln Lys Leu Leu Ala Gln Leu His His Arg Lys Arg Val Lys Ala -40 -35 -30 -25	
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Asn Asp Ser Gln Leu Ser Ala Ser Phe Leu Gln Pro Ser Leu Gln Ala
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Asp Phe Leu Arg Ser Leu Ser Asp Gly Asp Ser Gly Thr Ser Glu His
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                                40
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 Arg Leu Leu Pro Pro Pro Ser Leu Leu Ser Leu Glu Ala Pro Ala
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gtc	atc	cag	gag	Pro	cag	Cta	Cor	Len	Gln	Dro	Glu	Pro	Val	Phe	Thr	
Val	TIE	GIN	GIU	Pro	GIII	neu	5	пеа	GIII	110	014	10				
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Val	Asp	Arg	Ala	Glu	Val	Pro	Pro	Leu	Phe	Trp	Lys	Pro	Tyr	Ile	Tyr	
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gcg	ggc	tac	cgg	Pro	Lou	Wie	Gln	Thr	Trn	Ara	Phe	Tvr	Phe	Arg	Thr	
	GIY	IÀI	Arg	PIO	35	mria	QIII	****	115	40		-1-		5	45	
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Leu	Dhe	Gln	Cay	His	Asn	Glu	Ala	Val	Asn	Val	Trp	Thr	His	Leu	Leu	
Dea	FIIC	GIII	<b>U</b> 111	50	71011				55		-			60		
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gcc	tct	ttc	acc	tac Tyr	ctc	tcc	CCC	agt	712	Ley	λla	Hie	T.em	Leu	Gln	
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Glv	Val	Ala	Val	Tyr	Gln	Phe	Gly	Ser	Āla	Leu	Ala	His	Phe	Tyr	Tyr	
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гÀг	Tyr 175		GID	пλa	P.EO	180		₽¢u	GIY	n.y	185	-13				
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Pro	Ser	Val	Leu	Ala	Tvr	Ala	Leu	Asp	Ile	Ser	Pro	Val	Val	His	Arg	
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Ile	Phe	Val	Ser	Ser	Asp	Pro	Thr	Thr	Asp	Asp	Pro	Ala	Leu	ren	Tyr	
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cac	æag	tgo	cag	gtg	gto	: ttc	ttt	ctg	ctg	gct	gct	gcc	: דבכ	ττο	tct	643

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The Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly  240 245 230 240 245 235 236 236 236 236 236 237 237 240 245 255 260 236 245 255 260 265 265 265 265 265 265 265 265 265 265	a C C	ttc	ato	CCC	aaa	cac	taa	ttc		qqc	agc	tgc	cat	gtc	ttc	·ggg	873
240 245 250 agg gc cac cac act ttc cat atc ttc ttg gtg ctg tgc acg ctg gct sln Gly His Gln Leu Phe His Tle Phe Leu Val Leu Cys Thr Leu Ala 255 260 260 265 ag ctg gag gct gtg gca ctg gac tat gag gcc cac cac ctat till Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Tle Tyr 270 275 280 255 agg ctg gag gct gtg gca ctg gc ctat gag gcc cac acg ctt ctc ctc sln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Tle Tyr 270 275 280 265 agg ctg ct ctg cac acg cac tgg cct cac acc ttt tct ggc ctt tcc ctg 3cl up ro Leu His Thr His Trp Pro His Asn Phe Ser Gly Leu Phe Leu 290 295 300 ctc acg gtg ggc agc agc act ctc act gca ttc ctc ctg agc cag ctg Leu Thr Val Gly Ser Ser Tle Leu Thr Ala Phe Leu Leu Ser Gln Leu 305 310 315 gta cag cgc aaa ctt gat cag aag acc aag tgaagggggag tggcatctgg 11 cctggtaaag ttgt Leu Asp Gln Lys Thr Lys 320 325 tagggagggag ggtataagttg ggggacaggg gtctgggttt ggctccaagt gggaacaagg 12 cctggtaaag ttgtttgtgt ctggccaaaa aaaaaaaa 12 cctggtaaag ttgtttgtgt ctggccaaaa aaaaaaaa 12 cctgl Sig peptide 222> 3190 cc221> CDS c222> 31660 c221> sig peptide 222> 3190 cc223> Von Heijne matrix score 5.4  seq AFVIACVLSLIST/IY cc21> polyA site 222> 12881293 cc21> polyA site 222> 12881293 cctggaaggagg cgagcagtct gaatgccaga atg gat aac cgt ttt gct aca gca Met Asp Asn Arg Phe Ala Thr Ala -20 -15 ctt gta att gct tgt gtg ctt agc ctc att tcc acc act tac atg gca Phe Val Ile Ala Cys Val Leu Ser Leu Ile Ser Thr Ile Tyr Met Ala -10 -10 cct act ggc aca gac ttc tgg tat gag tat cga agt cca gtc cas Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln 5 cga aaat tcc agt gat ttg aat aaa agt att gga tga tc att agt Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 gat gag gca gat gas aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Asa Ser Glu Lys Thr Tyr Asn Asp Ala Leu Phe Ang Tyr Asn Asp Glu Lya Asp Glu Lya Asp Glu Lya Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Ang Tyr Asn	Chr	Phe	Met	Pro	Glu	Arg	Trp	Phe	Pro	Gly	Ser	Cys	His	Val	Phe	Gly	
and gag care cate text attert text styry gay and styry gay gay gay gay gay gay gay gay gay ga			240					245					250				
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ttt gta att gct tgt gtg ctt agc ctc acc att tcc acc atc tac atg gca         Phe Val Ile Ala Cys Val Leu Ser Leu Ile Ser Thr Ile Tyr Met Ala -10         gct tcc att ggc aca gac ttc tgg tat gag tat cga agt cca gtt caa         Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln 15         5       10         15       20         gaa aat tcc agt gat ttg aat aaa agc atc tgg gat gaa ttc agt Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25         gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn				-					Me	t As	p As	n Ar	g Ph	e Al	a Tr	r Ala	ì
Phe         Val         Ile         Ala         Cys         Val         Leu         Ser         Leu         Ile         Ser         Thr         Ile         Tyr         Met         Ala           gct         tcc         att         ggc         aca         gac         ttc         tgg         tat         gag         tat         cga         agt         cca         gtt         caa           Ala         Ser         Ile         Gly         Thr         Asp         Phe         Trp         Tyr         Glu         Tyr         Arg         Ser         Pro         Val         Gln           5         10         10         15         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20         20 <td< td=""><td>+++</td><td>ata</td><td></td><td>act</td><td>+ 0+</td><td>ato</td><td>ctt</td><td>ago</td><td>_</td><td>-</td><td>tee</td><td>acc</td><td>: atc</td><td>-</td><td></td><td>qca</td><td>102</td></td<>	+++	ata		act	+ 0+	ato	ctt	ago	_	-	tee	acc	: atc	-		qca	102
-10	Dhe	. yca	Tle	. gcc	Cvs	. yeş	Lei	. Ger	Leu	Ile	Ser	Thr	Ile	Туз	Met	Ala	
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Ala Ser Ile Gly Thr Asp Phe Trp Tyr Glu Tyr Arg Ser Pro Val Gln  5 10 15 20  gaa aat tcc agt gat ttg aat aaa agc atc tgg gat gaa ttc att agt Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser  25 30 35  gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn	qct	tec	att	aac	aca	gad	tto	: tgg	tat	gag	tat	: cga	agt	cca	gtt	caa	150
gaa aat tcc agt gat ttg aat aaa agc atc tgg gat gaa ttc att agt Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35 gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn	Ăla	Ser	Ile	Gly	Thr	Asp	Phe	rr	Tyr	Glu	туг	Arg	g Sei	Pro	Val	Gln	
Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser 25 30 35 gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn	5					10					15					20	198
gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn	gaa	aat	tc	agt	gat	ttg	aat	aaa	ago	ato	tgg	gat	gaa	l CC(	; att	. agt	130
gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn	GLu	Asr	ı Sei	ser		) rea	ASI	ı nys	ser		: rr]	AS[	וגיטיי		35		
Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn	a=+		י מרי	ים ה		. 220	ı acı	tat	aat		aca	a ctt	ttt	cq:		aat	246
	Asr	. yaş	ı Ala	. yat 1 Asr	Glu	LVS	Th	r Tyi	Asr	Asr	Ala	a Lei	ı Phe	Arg	ту	Asn	
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520

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					atc Ile -5											105
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                           -45
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                        -30
                                      -25
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15

20

Glu Asn Thr Tyr Thr Arg Ser Ala Glu Leu Thr Ala Ser Arg Leu Thr 30 35 40 Ala Thr Ser Thr Asp Gln Leu Glu Ala Leu Arg Asp Ile Leu His Asp

Ile Thr Pro Asn Val Leu Ser Phe Ala Leu Asp Phe Asp Glu Ala Thr

70 Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr 80 Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val 100 Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val 110 115 Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp 130 Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys 150 145 Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu 165 155 160 Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly 180 175

<210> 147 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -49..-1 <400> 147

Met Pro Gly Thr Glu Val Leu Glu Gly Ala Thr Asp Gly Leu Ala Ala
-45
-40
-35

Ile Asn Leu Leu Lys Trp Ile Lys Thr Leu Gly Gly Ser Val Ile Ser
-30
-25
-20

Met Ile Val Leu Leu Ile Cys Val Val Cys Leu Tyr Ile Val Cys Arg
-15
-10
-5

Cys Gly Ser His Leu Trp Arg Glu Ser His His
1

<210> 148 <211> 180 <212> PRT <213> Homo sapiens

<400> 148 Met Cys Ile Ser Gly Leu Cys Gln Ile Val Gly Cys Asp His Gln Leu 10 Gly Ser Thr Val Lys Glu Asp Asn Cys Gly Val Cys Asn Gly Asp Gly 25 20 Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr Lys Ser Gln Leu Ser Ala 35 40 45 Thr Lys Ser Asp Asp Thr Val Val Ala Ile Pro Tyr Gly Ser Arg His 60 55 Ile Arg Leu Val Leu Lys Gly Pro Asp His Leu Tyr Leu Glu Thr Lys 70 75 Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser Leu Ser Ser Thr Gly Thr 90 Phe Leu Val Asp Asn Ser Ser Val Asp Phe Gln Lys Phe Pro Asp Lys 105 110 100 Glu Ile Leu Arg Met Ala Gly Pro Leu Thr Ala Asp Phe Ile Val Lys 120 Ile Arg Asm Ser Gly Ser Ala Asp Ser Thr Val Gln Phe Ile Phe Tyr WO 99/31236 -118- PCT/IB98/02122

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135
                                140
Gln Pro Ile Ile His Arg Trp Arg Glu Thr Asp Phe Phe Pro Cys Ser
   150 155 · 160
Ala Thr Cys Gly Gly Gly Tyr Gln Leu Thr Ser Ala Glu Cys Tyr Asp
     165 170
Leu Arg Ser Asn
      180
<210> 149
<211> 162
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -23..-1
<400> 149
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Leu Ala Ala
    -20 -15 -10
Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu
 -5 1 5
Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
10 15 20 25
Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
         30
                        35
Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
                        50
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
             65 70
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
            95 100 105
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
            110 115 120
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Val Ser Met
         125 130
Val Phe
<210> 150
<211> 120
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 150
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Leu Ala Ala
      -20 -15 -10
Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu
    -5 1
Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
10 15 20
Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
```

35

Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
45
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
60
Cys Ile Arg Ser Lys Asn Gly Pro Gly Thr Ala Val His Ala Tyr Asn
75
Pro Ser Thr Phe Arg Gly Gln Val
90

<210> 151 <211> 7 <212> PRT <213> Homo sapiens <400> 151 Met Val Glu Met Thr Gly Val 1 5

<210> 152 <211> 199 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1

<400> 152 Met Asp Gly Gln Lys Lys Asn Trp Lys Asp Lys Val Val Asp Leu Leu -40 -35 -30 Tyr Trp Arg Asp Ile Lys Lys Thr Gly Val Val Phe Gly Ala Ser Leu -15 -20 Phe Leu Leu Ser Leu Thr Val Phe Ser Ile Val Ser Val Thr Ala -5 1 5 Tyr Ile Ala Leu Ala Leu Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr 10 15 20 Lys Gly Val Ile Gln Ala Ile Gln Lys Ser Asp Glu Gly His Pro Phe 25 30 Arg Ala Tyr Leu Glu Ser Glu Val Ala Ile Ser Glu Glu Leu Val Gln 40 45 50 Lys Tyr Ser Asn Ser Ala Leu Gly His Val Asn Cys Thr Ile Lys Glu 60 Leu Arg Arg Leu Phe Leu Val Asp Asp Leu Val Asp Ser Leu Lys Phe 75 Ala Val Leu Met Trp Val Phe Thr Tyr Val Gly Ala Leu Phe Asn Gly 90 95 Leu Thr Leu Leu Ile Leu Ala Leu Ile Ser Leu Phe Ser Val Pro Val 105 110 Ile Tyr Glu Arg His Gln Ala Gln Ile Asp His Tyr Leu Val Leu Ala 130 120 125 Asn Lys Asn Val Lys Asp Ala Met Ala Lys Ile Gln Ala Lys Ile Pro 145 135 140 Gly Leu Lys Arg Lys Ala Glu

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<211> 43
<212> PRT
<213> Homo sapiens
Met Pro Phe Arg Met Ser Gly Tyr Ile Pro Phe Gly Thr Pro Ile Val
                              10
Ser Val Thr Phe Lys Gly Phe Pro Phe Leu Lys Asn Tyr Phe Lys Cys
   20
                        25
Leu Thr Leu Cys Tyr Cys Ser Arg Val Phe Asp
<210> 154
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 154
Met Glu Trp Ala Gly Lys Gln Arg Asp Phe Gln Val Arg Ala Ala Pro
 -35 -30 -25
Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe
-20 -15 -10
Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala
-5 1 5
Gln Glu
<210> 155
<211> 153
<212> PRT
<213> Homo sapiens
<400> 155
Thr Val Pro Leu Leu Glu Pro Ala Asp His Ala Arg Gly Arg Ala
                  10
1 5
His Val His Leu Pro Glu Asn Val Arg Ser Gln Ser Pro Gly His Val
                         25
Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu
                       40 45
Lys Gln Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu
                   55
Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr
              70
                        75
Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser
                              90
Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys
                          105
Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly
      115 120 125
Glu Leu Lys Thr Glu Leu Leu Gly Leu Lys Glu Arg Lys His Lys Pro
                   135
Gln Val Ser Gln Gln Glu Glu Leu Lys
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<210> 156
<211> 67
<212> PRT
<213> Homo sapiens
<400> 156
Met Arg Gln Lys Arg Lys Gly Asp Leu Ser Pro Ala Lys Leu Met Met
                                  10
Leu Thr Ile Gly Asp Val Ile Lys Gln Leu Ile Glu Ala His Glu Gln
                              25
Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys
                       40
Tyr Gly Leu Ser Ala Gln Pro Arg Leu Val Asp Ile Ile Ala Ala Val
Pro Pro Glu
<210> 157
<211> 87
<212> PRT
<213> Homo sapiens
<400> 157
Met Asp Glu Leu Ser Glu Glu Asp Lys Leu Thr Val Ser Arg Ala Arg
                    10
Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val Ala Glu Val Phe
                              25
Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys Gly
                       40
Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln Ala
Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala Lys Ala Asp Lys
                             75
                   70
Leu Ala Glu Glu His Ser Ser
               85
<210> 158
<211> 250
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -85..-1
Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe Leu
                  -80
                                      -75
Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu Ile His
               -65
                                  -60
Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp
                              -45
Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr
                         -30 -25
Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
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-15

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

WO 99/31236 -122- PCT/IB98/02122 -

1 Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu 70 Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys 100 Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Ala Thr Ser Gln 115 Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr 130 135 Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg 145 Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn

<210> 159 <211> 24 <212> PRT <213> Homo sapiens

<210> 160 <211> 228 <212> PRT <213> Homo sapiens

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys 10 His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg 25 Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys 40 His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 55 60 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 70 75 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 90 85 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 120 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 135 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg

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150
                             155
Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu
                  170
       165
Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro
       180 185
Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln
                           205
     195 200
Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys
          215
                         220
Ser Thr Phe Ile
225
<210> 161
<211> 86
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<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1

<210> 162 <211> 44 <212> PRT <213> Homo sapiens

65

<210> 163 <211> 314 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1 <400> 163 Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala -55 -50 Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly -35 Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His -15 -20 His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys -5 1 Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro 10 . 15 Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala 30 Ile Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His 45 Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu 60 Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu 80 Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr 95 Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg 110 115 105 Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp 125 130 Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys 140 145 Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg 155 160 Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His 175 180 Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro 190 195 Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys 205 210 Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met 225 230 220 Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile 235 240 Glu Tyr Asp Tyr Thr Arg His Phe Thr Met

<210> 164 <211> 89 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -80..-1

<400> 164

 Met Arg Thr Arg Thr Thr Gly Asn Pro Arg Gly Leu His Asp Thr Phe

 -80
 -75
 -70
 -65

 Pro Arg Arg Pro Arg Leu Gly Arg Cys Ser Asp Met Asp Thr Ala Arg
 -60
 -55
 -50

 Thr Ser Cys Ser Asp Leu Leu Pro Trp Glu Gly Val Thr Glu Pro Ala
 -45
 -40
 -35

 Leu Cys Gly Asp Gln Leu Gln Gly Thr Glu Gly Trp Leu Glu Ala Thr

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-25
                                          -20
Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
 -15 -10
Ser Thr Gln Pro Val Pro Leu Cys Ser
1 5
<210> 165
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 165
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15 -10 -5
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
                           10
Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                     25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                   40
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
50 55
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu Thr Ser Glu Pro Leu
Thr Ala
<210> 166
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 166
Met Leu Val Thr Gln Gly Leu Val Tyr Gln Gly Tyr Leu Ala Ala Asn
-35 -30 -25
Ser Arg Phe Gly Ser Leu Pro Lys Val Ala Leu Ala Gly Leu Leu Gly
              <del>-</del>15
                                  -10
Phe Gly Leu Gly Lys Val Ser Tyr Ile Gly Val Cys Gln Ser Lys Phe
              1 5
His Phe Phe Glu Asp Gln Leu Arg Gly Ala Gly Phe Gly Pro Gln His
Asn Arg His Cys Leu Leu Thr Cys Glu Glu Cys Lys Ile Lys His Gly
                  35
Leu Ser Glu Lys Gly Asp Ser Gln Pro Ser Ala Ser
                50
<210> 167
<211> 351
<212> PRT
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WO 99/31236 -126- PCT/IB98/02122 -

<213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 167 Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -15 -10 Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10 Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile 25 Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40 Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 55 Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 70 75 Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 105 Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 120 Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 135 140 Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155 Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 165 170 Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 185 190 Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu 200 205 Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile 215 220 Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 235 Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp 245 250 Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser 260 265 Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val 275 280 285 Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys 295 300 His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys 310 315 His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg

330

<210> 168 <211> 138 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

325

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<400> 168 Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu -40 -35 -45 Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser -25 -20 Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile -10 -5 Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu 10 Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile 25 Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu 40 Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe 55 60 Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu 70 75 Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala

<210> 169 <211> 101 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -73..-1

<400> 169 Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg -65 Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val -50 -45 Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr -35 -30 Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe -15 -10 -20 Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile -5 1 5 Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile 10 15 Pro Leu Gly Thr Pro 25

Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 8.5 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys 175

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Glr. Glu Tyr Gln Gln Phe 70 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala WO 99/31236 -129- PCT/IB98/02122 ·

85 80 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 100 105 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 115 120 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 135 130 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 145 150 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 160 165 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 180 185 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 200 195 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 210 215 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 225 230 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 245 240 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 255 260 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser

<210> 172 <211> 390 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1 <400> 172 Met Pro Glu Gly Pro

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 -5 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 1 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His . 25 15 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 70 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 105 100 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115

Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 180 185 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 195 200 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 215 210 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Ser Lys Ala Thr Gln 230 225 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 245 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 260 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 290 295 300 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 305 310 Glu Gly Thr Ser Ala Ser 320

<210> 173 <211> 190 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1

<400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 -55 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 <del>-</del>25 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -15 -10 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 20 25 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 35 40 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 50 55 60 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

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95 100 105

<210> 174

<211> 285 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -232..-1 <400> 174 Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile -230 -225 -220 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu -215 -210 -205 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg -200 -195 -190 -185 Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu Leu -180 -175 -170 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg -165 -160 -155 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val -150 -145 -140 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile -135 -130 -125 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys -120 -115 -110 -105 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe -100 -95 -90 Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp -85 -80 -75 Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn -70 -65 Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile -35 -30 -25 Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala -20 -15 -10 Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val -5 1 5 Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu Ile 10 15 20 Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu 35 25 30 Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys 45 50

<210> 175 <211> 153 <212> PRT

<213> Homo sapiens

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25
Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg
                           40
                                              45
Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu
                       55
Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg
                                      75
                   70
Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val
                                  90
              85
Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile
                              105
          100
Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys
                          120
      115
Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys
                      135
His His Cys Val Arg Glu Gly Ser Gly
                   150
```

<210> 176 <211> 49 <212> PRT

<213> Homo sapiens

<210> 177
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL

<222> -24..-1 <400> 177

 Met
 Lys
 Ser
 Ala
 Lys
 Leu
 Gly
 Phe
 Leu
 Leu
 Arg
 Phe
 Phe
 Ile
 Phe
 Cys

 Ser
 Leu
 Asn
 Thr
 Leu
 Leu
 Leu
 Gly
 Val
 Asn
 Lys
 Ile
 Ala
 Glu
 Lys

 Ile
 Cys
 Gly
 Asp
 Pro
 Cys
 Lys
 Leu
 Asn
 Phe
 Gly
 Asn
 Met
 Asn
 Phe
 Gly
 Ile
 Asn
 Phe
 Gly
 Ile
 Asn
 Asn
 Phe
 Gly
 Ile
 Asn
 Asn
 Phe
 Gly
 Ile
 Asn
 Asn

Pro Pro Arg 75

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<210> 178
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
     -35
                        -30
                                          -25
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
                    -15
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
                         5
              1
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
                  20
      15
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
              35
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
           50
<210> 179
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Phe Leu Leu Phe Phe Phe
                    -15 -10
       -20
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
      -5
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
                 15
                      20
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
             30
                               35
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
              50
          45
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
                        65
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
                    80
Gln Lys Leu Ala Lys Lys Met Phe Phe
<210> 180
<211> 59
<212> PRT
<213> Homo sapiens
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<400> 180

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

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<210> 181 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 181 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 -5 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Pro Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly Tyr Arg Ile Cys Asp Leu

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

70

<400> 182 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -15 -25 -20 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val 1 - 5 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe Leu 15 20 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 Ser Leu Gln Asp Ala Leu Leu Leu Leu Met Gly Leu Gly Pro Leu

```
80
 Leu Arg Ala Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys
                  95
        90
 Leu His Pro Trp Ala
      105
 <210> 183
 <211> 80
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -35..-1
 <400> 183
 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
 -35 -20 -25 -20
Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ser Ala Ala
                     -10
 Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
 Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
  15 20
                           25
 Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys
 30 35 40 45
 <210> 184
 <211> 73
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -21..-1
 <400> 184
 Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
  -20 -15
                                  -10
 Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
 -5
              1 5
 Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
       15 20 25
 Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
                                 40
               35
 Cys Gly Asn Ile Cys Met Ser Ile Leu
   45
              50
 <210> 185
 <211> 98
 <212> PRT
 <213> Homo sapiens
 <400> 185
 Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
              5
```

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 The Ser Lys
 Arg 20
 Glu Gln Leu Glu Gln Gln Gln Val Pro Glu Asn Tyr
 Phe 30

 Tyr
 Val Pro Asp Leu Gly Gln Val Pro Glu Ile Asp Val Pro Ser Tyr 35
 40
 40
 45

 Leu Pro Asp Leu Pro Gly Ile Ala Asn Asn Asp Leu Met Tyr Ile Ala Asp 50
 55
 60

 Leu Gly Pro Gly Ile Ala Pro Ser Ala Pro Gly Thr Ile Pro Glu Leu 65
 70
 75

 Pro Thr Phe His Thr Glu Val Ala Glu Pro Bro Glu Pro Gly Tyr
 10
 10

 Gly Tyr
 10
 10
 10
 10

<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 186 Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe Gly Leu -10 -15 Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile Asp Val 1 5 Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg Gln Val 20 Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Asp Thr Pro 35 Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu Gln Phe Phe Gln Lys 50 Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val Thr Leu Lys Gln Thr 70 65 His Leu Asn Ser Gly Val Ile Leu Ser Ile His His Leu Asp His Arg

<210> 187 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -44..-1

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<210> 188
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 188
Met Leu Phe Ser Leu Ser Leu Ser Asn Leu Asn Gln Ile Gly Ser
    -10 -5
Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                                      15
                    10
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
                25
                                  30
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
              40
                               45
Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg
                        60
Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys
<210> 189
<211> 207
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 189
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
                        -35
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                     -20
                               -15
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile
              -5
                           1 5
Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
                         15 20
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys
                      30
Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met
                                      50
  40
                   45
Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu
                60
                                   65
Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile
              75
                               80
Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu
                            95
          90
Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys
                        110
                                           115
Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro
```

125

Ala Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr

140

Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu

145

120

155 160 165

```
<210> 190
<211> 201
<212> PRT
<213> Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                10 15
1 5
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
             25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
             40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
            55
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
             70 75
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
                           90 95
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
        100 105 110
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
   115 120
Thr Met Glu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
 130 135
Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu
145 150 155 160
Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg
           165 170
Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr
Asp Thr Val Lys Ile Gln Lys Lys
```

<210> 191

<211> 379

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 191

Met Pro His Ser Ser Leu His Pro Ser Ile Pro Cys Pro Arg Gly His
-35 -30 -25

Gly Ala Gln Lys Ala Ala Leu Val Leu Leu Ser Ala Cys Leu Val Thr
-20 -15 -10

Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val -5 1 5 10

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Leu Asn Gly Val Cys
15 20 25

Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser 30 40

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly
45 50 55

Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala

```
65
                           70
Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln
          80
                  85 90 ·
Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile
             100 105
Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala
          115 120
Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln
        130 135
Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
     145 150
Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val
    160 165 170
Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys
                     180
     175
Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr
190 195
Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr
                210 215
Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser
             225
                           230 235
Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala
           240 245 250
Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu
       255
                     260 265
Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp
    270 275
Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu
  285 290
                              295
Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro
300 305
                           310
Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met
        320 325
Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser
```

<210> 192 <211> 112 <212> PRT <213> Homo sapiens

<400> 192

Met Pro Ser Glu Gly Arg Cys Trp Glu Thr Leu Lys Ala Leu Arg Ser 10 Ser Asp Lys Gly Arg Leu Cys Tyr Tyr Arg Asp Trp Leu Leu Arg Arg 25 20 Glu Asp Val Leu Glu Glu Cys Met Ser Leu Pro Lys Leu Ser Ser Tyr 40 Ser Gly Trp Val Val Glu His Val Leu Pro His Met Gln Glu Asn Gln 55 Pro Leu Ser Glu Thr Ser Pro Ser Ser Thr Ser Ala Ser Ala Leu Asp 70 75 Gln Pro Ser Phe Val Pro Lys Ser Pro Asp Ala Ser Ser Ala Phe Ser 85 90 Pro Ala Ser Pro Ala Thr Pro Asn Gly Thr Lys Gly Lys Lys Lys

```
<211> 43
<212> PRT
<213> Homo sapiens
Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser
                                 10
Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn
Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys
<210> 194
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 194
Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
                   -10 -5
Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
                      10
Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
                    25
Pro Asn Phe
     35
<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195
Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala
                           -10
Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser
Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile
                 20
                                   25
Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys
                                 40
Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp
                             55
Val Thr Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly
                         70
Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala
                     85
                                        90
```

Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

100

115 120 Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro 135 140 130 Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln 150 155 Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp 170 165 Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro 180 185 His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val 195 200 205 Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly Arg Thr Ala Trp 225

<210> 196 <211> 353 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -25 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln 1 5 Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 20 25 Ala Gly Pro Leu Ala Val Ala Ala Val Leu Tyr His Lys Met Asn Asn 40 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 75 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 115 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 135 Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 145 150 155 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 185 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 210 215 220 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly

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```
Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr
                      245 250
Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys Lys
                                     265
Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr Pro
               275 280
Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe
                  295
Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu
                         310
Leu
<210> 197
<211> 30
<212> PRT
<213> Homo sapiens
<400> 197
Met Gln Met Asp Thr Phe Phe Met Ser Glu Lys His Thr His Thr His
                                 10
Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys
                              25
<210> 198
<211> 112
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1
<400> 198
Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly
                           -40
Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala
 -30
                          -25
Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala
                   -10
Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val
                                 10
Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe
          20
                             25
Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser
                          40
Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His
                     55
<210> 199
<211> 54
<212> PRT
<213> Homo sapiens
Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr
```

 Pro
 Arg
 Trp
 His
 Arg
 Leu
 Pro
 Pro
 Gln
 Ser
 Leu
 Gln
 His
 Gln
 Tyr

 Cys
 Gln
 Arg
 Arg
 Trp
 Pro
 Asp
 Arg
 Arg
 Cys
 Leu
 Gln
 Ser
 His
 Thr
 Gln

 Ser
 Ser
 Gly
 His
 Leu
 Pro
 45
 Frage
 Frage

<210> 200 <211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21...1

<400> 200

Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 -10 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile -5 1 5 Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 15 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 40 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp 50 ..55 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 65 70 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 80 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 100 105 Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn 110 115 Gly Lys Val Lys Ser Phe Lys

<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1 <400> 201

125

 Met
 Ser
 Met
 Ala
 Val
 Glu
 Thr
 Phe
 Gly
 Phe
 Ala
 Thr
 Val
 Gly
 Phe
 Phe</th

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```
Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Leu Gly
          60 65
Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg
Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly
                    95
                            100
Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg
           110
                           115
Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro
      125 130 135
Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly
      140 145 150
Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala
   155 160 165
Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val
  170 175
Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg
                 190
Asn Ala Tyr Val
200
```

<210> 202 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

<210> 203 <211> 146 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1 <400> 203

Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile Asp Arg Glu Asn 40 45 Phe Val Asp Ile Val Asp Ala Lys Leu Lys Ile Pro Val Ser Gly Ser 60 55 Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg Gly Gly Pro Phe 75 70 Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu Lys Asp Gly Gln 90 Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly Asp Glu Val Lys 105 Lys Glu 115

<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<400> 204

Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser Leu 10 Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His Leu 25 20 Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro Glu 40 Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser 55 60 Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu 70 Glu Val Asp Asp Trp Glu Phe 85

<210> 205 <211> 40 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1

<400> 205 Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -25 -20 -15 Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -10 -5

Leu Ser Leu Arg Ser Ala Met Ser 10

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206 Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg

```
10
Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser
Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro
             40
Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr
         55
Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu
      70 75
Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys
      85 90 95
Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val
     100 105 110
Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg
    115 120 125
His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys
 130 135
Glu Glu Ala Ala Met Lys Ala Lys Thr Glu
```

<210> 207 <211> 101 <212> PRT

<213> Homo sapiens

Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr
85
90
95

Lys Gln Thr Ser Val

<210> 208 <211> 456 <212> PRT

<213> Homo sapiens

<220>
<221> SIGNAL
<222> -22..-1

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```
40
                       3.5
Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
                         55
           50
Phe Ala Ser Ala Ser Ala Glu Val Gly Lys Lys Gly Lys Lys Cys
              65
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
                   85
     80
Lys Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
               100 105
        95
Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
       110 115 120
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
    125 130 135
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
      145
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
             160 165
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
           175 180 185
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
        190
                      195
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
     205 210 215
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
  220 225
                               230
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
             240
                            245
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
           255
                         260
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
                      275
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
                   290 295
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
                305 310
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
                            325 330
             320
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                         340 345
          335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
        350 355 360
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
     365 370
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
  380 385
                               390
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
395 400 405 410
Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
                  420
        415
Gln Pro Cys Leu Tyr Lys Arg Arg
        430
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<210> 209 <211> 98 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -17..-1 WO 99/31236 -148- PCT/IB98/02122 .

<400> 209 Met Pro Ser Ser Phe Phe Leu Leu Leu Gln Phe Phe Leu Arg Ile Asp -15 -10 -5 Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp 1 5 10 15 Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser 20 25 Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile 35 . 40 Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe 50 55 Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln Val Glu 80 <210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1 <400> 210 Met Thr Leu Leu Ser Phe Ala Ala Phe Thr Ala Ala Phe Ser Val Leu -25 -20 Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg Ala Leu Ala Ser Val Phe -5 -10 Asp Pro Leu Cys Val Cys Ser Arg Val Leu Pro Thr Pro Val Cys Thr 10 Leu Val Ala Thr Gln Ala Glu Lys Ile Leu Glu Asn Gly Pro Cys Pro 25 30 Thr Lys Glu Ala Ala Gln Leu Val Gly Lys Gly Ser Val Ser Ala Arg 45 40 Asn Ala Ser <210> 211 <211> 229 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -23..-1

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50
        45
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
                           70
              65
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                 80
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn
                     100 105
           95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
      110 115 120
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile
                       130 135
        125
Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu
                         150
                    145
Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe
                       165
 155 160
Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val
170 175
Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys
                   195
    190
Arg Lys Ser Arg Thr
        205
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<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly 1 Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 20 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 35 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 50 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val 70 65 Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 80 Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 100 105 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 Asn Asp Phe Ser Gln Glu Ser Ser 125

<210> 213 <211> 179 <212> PRT <213> Homo sapiens WO 99/31236 -150- PCT/IB98/02122 -

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<220>
<221> SIGNAL
<222> -54..-1
<400> 213
Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr
                  -45
Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala
                 -30
Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Val Ala Ala Ala Ala
                    -15
                              -10
Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys
                        5 10
         1
Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro
                            20
      15
Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu
                         35
Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu
                      50
Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu
                           70
Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser
                80
                        85
Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp
            95
                             100
Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met
                  115
Asn Leu Ile
     125
<210> 214
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<210> 214
<211> 269
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -92..-1
<400> 214
Met lle Thr His Val

Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu -90 -85 Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro -75 -70 -65 Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp -60 -55 **-**50 -45 Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr -40 -35 Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala -25 -20 Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val -5 Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val 10 15 Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe 30 25 Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys 4.5 His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr <210> 215 <211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

110

<400> 215

<210> 216

Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -20 -15 -10 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala -5 1 5 10 Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 15 20 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu 65 70 Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 80 85 90 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 100 105 95 Ser Ala Pro Lys Ser Asn Val

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<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1 <400> 217

Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu
-50

Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Gln Glu Ala
-35

Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu
-20

Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro
-5

Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr
15

Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Gln Ile Leu
30

Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn
45

Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Asp Tyr

<210> 218 <211> 376 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 218 Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Pro Pro -15 Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro 1 Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile Gly 20 Thr His Asn Gly Thr Phe His Cys Asp Glu Ala Leu Ala Cys Ala Leu 35 Leu Arg Leu Leu Pro Glu Tyr Arg Asp Ala Glu Ile Val Arg Thr Arg 50 Asp Pro Glu Lys Leu Ala Ser Cys Asp Ile Val Val Asp Val Gly Gly 65 70 Glu Tyr Asp Pro Arg Arg His Arg Tyr Asp His His Gln Arg Ser Phe 80 85 Thr Glu Thr Met Ser Ser Leu Ser Pro Gly Arg Pro Trp Gln Thr Lys

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```
100
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
            115 . 120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                 130
                                  135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
              145
                               150
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
                           165 170
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
                        180 185
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
          195
                             200
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
  205 210 215
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
      225 230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
            240 245
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
              260
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
     270 275
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
                  290
                                 295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
               305
                               310
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
            320 325 ... 330
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
         335 340
Arg Ser Tyr Leu Pro Gln Ile Ser
      350
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<210> 219
<211> 211
<212> PRT
<213> Homo sapiens
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<400> 219

<221> SIGNAL <222> -30..-1

Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val -25 -20 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Pro -5 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 15 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 75 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe 90

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```
His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro
 100 105
Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser
             120
                       125
Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly
            135
                            140 145
Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser His Ser
        150
             155
Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser
 165 170
Arg Gln Leu
  180
<210> 220
<211> 154
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 220
Met Gly Ser Lys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu
         -55
Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys
          -40
                  -35 ⋅⋅ -30
Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
        -25 -20 -15
Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
   -10 -5 1
Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln
         10 15 20
Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu
           25
                  30 35
Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met
                       45
Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe
              60
Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln
                75
Pro Glu Phe His Ile Glu Ile Leu Ser Ile
               90
<210> 221
<211> 123
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
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Met Lys Gly Gly Ala Phe Ser Asn Leu Asn Asp Ser Gln Leu Ser Ala
-40 -35 -30

Ser Phe Leu Gln Pro Ser Leu Gln Ala Asn Cys Pro Ala Leu Asp Pro
-25 -20 -15

<400> 221

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<210> 222 <211> 346 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 222 Met Ala Met Ala Gln Lys Leu Ser His Leu Leu Pro Ser Leu Arg Gln -15 -10 Val Ile Gln Glu Pro Gln Leu Ser Leu Gln Pro Glu Pro Val Phe Thr 5 Val Asp Arg Ala Glu Val Pro Pro Leu Phe Trp Lys Pro Tyr Ile Tyr 20 25 Ala Gly Tyr Arg Pro Leu His Gln Thr Trp Arg Phe Tyr Phe Arg Thr 35 40 Leu Phe Gln Gln His Asn Glu Ala Val Asn Val Trp Thr His Leu Leu 55 Ala Ala Leu Val Leu Leu Arg Leu Ala Leu Phe Val Glu Thr Val 70 Asp Phe Trp Gly Asp Pro His Ala Leu Pro Leu Phe Ile Ile Val Leu 85 Ala Ser Phe Thr Tyr Leu Ser Leu Ser Ala Leu Ala His Leu Leu Gln 100 Ala Lys Ser Glu Phe Trp His Tyr Ser Phe Phe Phe Leu Asp Tyr Val 115 120 Gly Val Ala Val Tyr Gln Phe Gly Ser Ala Leu Ala His Phe Tyr Tyr 130 135 140 Ala Ile Glu Pro Ala Trp His Ala Gln Val Gln Ala Val Phe Leu Pro 150 Met Ala Ala Phe Leu Ala Trp Leu Ser Cys Ile Gly Ser Cys Tyr Asn 165 Lys Tyr Ile Gln Lys Pro Gly Leu Leu Gly Arg Thr Cys Gln Glu Val 180 185 Pro Ser Val Leu Ala Tyr Ala Leu Asp Ile Ser Pro Val Val His Arg 195 200 Ile Phe Val Ser Ser Asp Pro Thr Thr Asp Asp Pro Ala Leu Leu Tyr 210 215 His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Phe Phe Ser 230 Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly 245 Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala 260 265

Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

```
275
                                  280
Glu Pro Leu His Thr His Trp Pro His Asn Phe Ser Gly Leu Phe Leu
                      295 300<sup>°</sup>
        290
Leu Thr Val Gly Ser Ser Ile Leu Thr Ala Phe Leu Leu Ser Gln Leu
         305
                  310
Val Gln Arg Lys Leu Asp Gln Lys Thr Lys
      320
              325
<210> 223
<211> 210
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 223
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
-20 -15 -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
              1 5
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
     15
             20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                    35
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
                50
                                   55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                               70
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                        100
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                     115
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
                 130
                                  135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
             145 150
His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu
                           165
                                            170
Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys
Pro Lys
  190
<210> 224
<211> 184
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
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Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser

<400> 224

-15 -10 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp 1 Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 65 Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 95 100 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 145 150 His Leu Leu Ala Asp Thr Met Leu

<210> 225 <211> 227 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -22..-1

<400> 225

Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu -20 -15 -10 Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 80 85 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile 95 100 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 115 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 130 135 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 145 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 160 165 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala 175 180

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Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile
   190 195
Ala Ala Cys
     205
<210> 226
<211> 74
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 226
Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu
                              -30
  -40 -35
Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr
                       -15
      -20
Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg
          -5 1 5
Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile
             15
Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu
   25
                    30
<210> 227
<211> 73
<212> PRT
<213> Homo sapiens
<400> 227
Met Glu Lys Tyr Glu Asn Leu Gly Leu Val Gly Glu Gly Ser Tyr Gly
1
          5
                 10
Met Val Met Lys Cys Arg Asn Lys Asp Thr Gly Arg Ile Val Ala Ile
         20
                          25
Lys Lys Phe Leu Glu Ser Asp Asp Lys Met Val Lys Lys Ile Ala
                      40
                                       45
Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg His Glu Asn Leu Val
                   55
Asn Leu Leu Glu Val Cys Lys Lys
<210> 228
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 228
Met Lys Arg Leu Leu Pro Ala Thr Ser Leu Ala Gly Pro Val Leu Ser
           -10
                              -5
 -15
```

Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp

5 10 Asp Leu Phe Leu Phe Phe Lys Ser His Lys Thr Trp Gly Ile Ser Thr 25 20 Asn Leu Ser Ser Cys Pro Phe Gly Asn Leu Phe Leu Cys Val Gln Phe 40 Val Arg Glu Lys Gln Ser Phe Cys Met Asn Thr Glu Cys Asp Leu Arg 55 Lys Asn 65

<210> 229 <211> 119 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -56..-1 <400> 229 Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser Ser -55 -50 -45 Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly -35 -30 Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp -20 -15 -10 Ser Phe Val Ser Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr -5 1 5 Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu 15 Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly

Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro

50

25 30 35

Ile Leu Ala Lys Lys Lys 60

<210> 230 <211> 54 <212> PRT <213> Homo sapiens Ala Phe Val Trp Glu Pro Ala Met Val Arg Ile Asn Ala Leu Thr Ala 10 Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys 25 Asn Pro Arg Ser Thr Val Asp Ala Pro Thr Ala Ala Gly Arg Gly Arg 35 40 Gly Arg Gly Arg Pro His

<210> 231 <211> 210 <212> PRT

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<213> Homo sapiens

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<221> SIGNAL
<222> -14..-1
<400> 231
Met Leu Thr Leu Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val
          -10 -5
Gly Gly Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr
                      10
Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu
                 25
Arg Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile
                40
                                45
Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe
                             60
Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met
                         75
Thr Ala Tyr Leu Asp Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu
               90
Asn Thr Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly
             105
Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu
115 120 125
Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile
          135 140 145
Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg
        150 155 160
Arg Asp Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp
                            175
     165 170
Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys
         185
Gln Glu
195
```

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<210> 232
<211> 108
<212> PRT
<213> Homo sapiens
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<220>

<400> 232 Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Cys Ile Phe Lys Ile 10 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu 20 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 35 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu Leu 55 60 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 75 70 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90

Leu Pro Glu Glu Pro Lys Gly Thr Gln Met Leu Thr 100 105

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 233
Met Ser Ser Gly Arg Leu Arg Trp Leu Met Pro Val Ile Pro Ala Leu
 -15 -10
Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
 1 5
Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr
15 20 25
<210> 234
<211> 36
<212> PRT
<213> Homo sapiens
<400> 234
Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg Leu
1 5
                          10
Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys Thr
  20
Phe Phe Gln Ile
   35
<210> 235
<211> 307
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 235
Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu Gly Ala Met Met Leu
     -10 -5 1
Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro
Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu
               25
                               30
Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile
            40
Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu
                         60
Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe Gly Ser Gly Pro Cys
                      75
Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg
                90
Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu
    105
Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser
            120 125 130
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Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr 135 140 145

Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 150 155 160 Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 185 190 195 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 200 205 210 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 215 220 225 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 230 235 240 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 260 265 270 275 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala 285 Lys Lys Lys

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Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
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Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
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Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
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Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn
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Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp
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-10

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Pro Pro Leu Xaa Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro
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Phe Cys Pro Pro Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp
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Lys Tyr Ser Asn Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu
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tct cca ttg gaa caa aag ctt aga aaa tta aga caa gaa aca caa gaa
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Ser Pro Leu Glu Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu
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Trp Asn Gln Gln Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu
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Lys Glu Glu Phe Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu
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Arg Thr Glu Ser Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala
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Lys Lys Arg Ser Asn
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Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
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Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
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Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
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Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
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Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp Leu Tyr	
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Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser Gln Lys	200
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Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val	412
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ata	ctc	ctc	tcc	aaa	tca	aaa	tcc	aac	cct	cta	aga	aac	aaa	gaa	ata	57	8
	145		Ser			150					155						
aaa	gaa	gac	tca	caa	aag	aag	aag	agt	gct	cgg.	cgt	att	ttt	cag	gaa	62	6
ьуs 160	GIU	Asp	Ser	Gin		Lys	Lys	Ser	Ala		Arg	Ile	Phe	Gln			
	act	caa	gaa	cta	165	cat	220	202	an+	170	~~~				175	<b>6</b> 7	
Ile	Ala	Gln	Glu	Leu	Tvr	His	Lvs	Ara	His	Val	Glu	Thr	Asn	Gln	Gln	67	4
				180					185					190	<b></b>		
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Ser	Glu	Lys	Asp 195	Asn	Asn	Thr	Tyr	Glu 200	Asn	Arg	Arg	Val	Leu 205	Ser	Asn		
tat Tyr	gaa Glu	agg Arg 210	cca Pro	taga	aacg	itt t	taat		a at	gaag	tcac	tga		cca		77	4
acto	cago		tatg	gcag	t gt	taat	gaac	ata	tato	atc	aggt	ctta	aa a	aaaa	ataaa	83	4
ggta	aact	ga a	aaga	caac	t gg	ctac	aaag	, aag	gatg	cca	raat	gtaa	gg a	aact	ataac	89	
taat	akto	at t	acca	aaat	a ct	aaaa	ссса	aca	aaat	gca	actg	aaaa	at a	cctt	ccaaa	95	4
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Thr Arg Val Glu Ser Glu Lys Cys Asn Asn Leu Trp Leu Phe Leu Glu	
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20	364
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cogoogaa gogogaaaa amaaagaa agaasaa aaaaa	484
gacetgeed ggaggeegga geagaaaggg ceeecoocgg ggaggagaa ceeecoocgg	544 604
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Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe	
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tot acc off ggg aag oof gat ooc ggt gtg tgg ooc ago ftg tto agg	329
Ser Thr Leu Gly Lys Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg	
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ccc tgg gat gct gca tct cca ggc aac tat gca ctt tcc cgg gga rar Pro Trp Asp Ala Ala Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa	5,,
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aac cak tat gav aak tgg ggg cag ggc aca cat tca tct ttg	419
Asn Xaa Tyr Xaa Xaa Trp Gly Gln Gly Thr His Ser Ser Leu	
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gacctgcttt gccattctcc tggtgccgct gctgctccct gtttctggag ctggatgttc	539
cccacctggc agttgagctg cctgagccaa tgtgtctgtc tttggtaact gagtgaacca	599
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                                                                    120
ag atg ccc tgt cca acg tgg acc tgc ttg aag agc ttc ccc tcc ccg
                                                                    167
  Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro
acc agc agc cat gca tcg agc ctc cac ctt cct cca tca tgt acc agg
                                                                    215
Thr Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg
                           5
                                                                    263
cta act ttg aca caa act ttg agg aca gga atg cat ttg tca cgg gca
Leu Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala
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ttg caa ggt aca ttg acc agg cta cag tcc act cca gca tgaatgarat
                                                                    312
Leu Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala
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                                       40
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gctggaggaa ggacatgakt atgeggtcat gctgtacacc tggegeaget gtteeeggge
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cattccccag gtgaaatgca acragcagcc caaccgakta raratctatg araaracagt
araggtgctg gagccggagg tcaccaagct catgaagttc atgtattttc arcgcaaggc
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                                                                    552
categagegg ttetgeaseg aggtgaageg getgtgeeat geegagegea ggaaggaett
tgtctctgag gcctacctcc tgacccttgg caagttcatc aacatgtttg ctgtcctgga
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1315
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<sup>&</sup>lt;211> 1035

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atc tcc atc ttc cct act atg atg gtg tgt atg atg gcc tgg cga ccc
Ile Ser Ile Phe Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro
                  -55
                                        -50
att cag gca ctt atg gcc att tca gcc act ttc aag atg tta gaa agt
Ile Gln Ala Leu Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser
                -40
                                    -35
tca agc cag aag ttt ctt cag ggt ttg gtc tat ctc att ggg aac ctg
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Ser Ser Gln Lys Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu
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                                -20
atg ggt ttg gca ttg gct gtt tac aag tgc cag tcc atg gga ctg tta
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Met Gly Leu Ala Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu
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cct aca cat gca tcg gat tgg tta gcc ttc att gag ccc cct gag aga
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Pro Thr His Ala Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg
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                                        15
atg gag tca gtg gtg gag gac tgc ttt tgt gaa cat gag aaa gca gcg
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Met Glu Ser Val Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala
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cct ggt ccc tat gta ttt ggg tct tat tta cat cct tct tta agc cca
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Pro Gly Pro Tyr Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro
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gtg gct cct cag cat act ctt aaa cta atc act tat gtt aaa aaa aac
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Val Ala Pro Gln His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn
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Gln Lys Thr Leu Phe Ser Met Val Gly
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gtc ctc atg ggc tta cct ctg gcc cag gcc ttg gac tgc cac gtg tgt
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Ala Tyr Asn Gly Asp Asn Cys Phe Asn Pro Met Arg Cys Pro Ala Met
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                               15
gtt gcc tac tgc atg acc acg cgc acc tac tac acc ccc acc agg atg
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Val Ala Tyr Cys Met Thr Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met
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Lys Val Ser Lys Ser Cys Val Pro Arg Cys Phe Glu Xaa Cys Val
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Cys Gly Ser Leu Leu Pro Gly Leu Trp Gln His Leu Thr Ala Asn His

-10

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Trp Pro Pro Phe Ser Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser  10 15 20	
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25 30 35	
too otg aac caa gag coa tto gty toa aga goo att ogt coa aag tac	422
Ser Leu Asn Gln Glu Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr 40 45 50	
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Ser Ile Thr 55	
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Ser Gly Asn Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys 65 70 70 75  ccc ata tct tgc cga aat gta aat ggc tat tcc tac aat gag cag tcg 386  Pro Ile Ser Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser 80 85 90  cat gtc tct ttt tct tgg atg gtt ggg agc aga tcg att tta cct tgg 434  His Val Ser Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp 95 100 105 110  ata ccc tgc ttt ggg ttt gtt aaa btt tyg cac tgt agg gtt tkg tgg 482  Ile Pro Cys Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp 115 120 125  aat tgg gag cct aat tgattcaty cttattcaa tgcagattgt tggacctca 537  Asn Trp Glu Pro Asn 130  aatggaagta gttacattat agattactat ggaaccagac ttacaagact gagtattact 597  aatggaagta gttacattat agattactat ccataaatat tttttaaaag aaacagattt 657  gagcctcctt gattttaata gagaacttct agtgtatgga tttaaagatt tctcttttc 717  attcatatac cattttatga gttctgtata atttttgtg gttttgttt tgttgagtta 777  aagtatatta ttgtgagatt tatttaatag gacttccttt gaaagctgta taatagtgtt 837  tctcgggctt ctgtctctat gagagatagc ttattactct gatacttat catacttttac 897  aaaggcaagt tgccacttgt catttttgtt tctgaaaaa aaaagtataa cttattcaca 957				50	•				55				•	60	•		
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agagcaagtg gaatctctaa ga atg gct tcc agc cac tgg aat gaa acc act	172
Met Ala Ser Ser His Trp Asn Glu Thr Thr	
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Thr Ser Val Tyr Gln Tyr Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro	
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ata ttt aca gtg gta tct tta gtg gtg ctg gct ttc ctt tat gaa gtg	316
Ile Phe Thr Val Val Ser Leu Val Val Leu Ala Phe Leu Tyr Glu Val	
-5 1 5 10	264
ctt gam wgc tgc tgc tgt gta aaa aac aaa acc gtg aaa gac ttg aaa	364
Leu Xaa Xaa Cys Cys Cys Val Lys Asn Lys Thr Val Lys Asp Leu Lys	

15 20	25
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Ser Trp Trp Cys His Val Leu Glu Val Val Lys	Gly Gln Met Phe Thr
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Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu -10 -5	1
tat gcc tcg ggt act tat ttc cta ata tat atc	agc aca gta acg cct 439
Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile	Ser Thr Val Thr Pro
5 10 15	20
age tgg agg ett tgt ett gtt agt tgataaatta	gtggtaacag gtagatttgg 493
Ser Trp Arg Leu Cys Leu Val Ser 25	
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                                                                      176
                                              Met Glu Asp Pro Asn
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cct gaa gag aac atg aag cag cag gat tca ccc aag gag aga agt ccc
Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro Lys Glu Arg Ser Pro
                                    -65
                -70
cag age cca gga gge aac ate tge cae etg ggg gee eeg aag tge ace
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Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly Ala Pro Lys Cys Thr
            -55
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cgc tgc ctc atc acc ttc gca gat tcc aag ttc cag gag cgt cac atg
Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe Gln Glu Arg His Met
                            -35
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aag cgg gag cac cca gcg gac ttc gtg gcc cag aag ctg cag ggg gtc
Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln Lys Leu Gln Gly Val
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    -25
ctc ttc atc tgc ttc acc tgc gcc cgc tcc ttc ccc tcc taa gcc
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Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe Pro Ser Ser Lys Ala
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ckr rkc acc cac car cgc agc cac ggt cca rcc gcc aag ccc acc ctg
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Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa Ala Lys Pro Thr Leu
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ccg gtt gca acc act act gcc car ccc acc ttc cct tgt cct gac tgt
Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe Pro Cys Pro Asp Cys
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Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa Arg His Xaa Gln Xaa
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cat gar gtc cgt gcc cct cct ggc acc ttc gcc tgc aca rad tgc ggt
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His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala Cys Thr Xaa Cys Gly
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Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln His Tyr Ile Arg His
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Ala Arg Gly Gly Leu
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                            -60
gga gtg agc ctt cca gga att ttg gct gcc aaa tgt ggt gca gaa gta
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Gly Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val
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Ile Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg
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-35
                    -30
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caa agc tgc caa atg aat aac ctg cca cat ctg cag gtg gta gga cta
Gln Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu
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                -15
aca tgg ggt cat ata tct tgg gat ctt ctg gct cta cca cca caa gat
Thr Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp
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att atc ctt gca tct gat gtg ttc ttt gaa cca gaa rat ttt gaa gac
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Ile Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp
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att ttg gct aca ata tat ttt ttg atg cac aar aat ccc aag gtc caa
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Leu Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala
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tta ctc tac aaa tgg gat atg aaa tgt gtc cac att cct ctt gag tct
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Phe Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg
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His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu
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gtg cag aac ccc ggc gcg gcc ctt gac ctt tgc att gca gct gta att Val Gln Asn Pro Gly Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile -30 -25 -20	149
aaa gaa tgc cat ctc gtc ata ctg tcg ctg aag agc caa acc tta gat Lys Glu Cys His Leu Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp -15 -10 -5	197
gca gaa aca gat gtg tta tgt gca gtc ctt tac agc aat cac aac aga Ala Glu Thr Asp Val Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg 1 5 10 15	245
atg ggc cgc cac aaa ccc cat ttg gcc ctc aaa cag gtt gag caa tgt Met Gly Arg His Lys Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys 20 25 30	293
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Ser Pro Gln Ala Leu Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser
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Ile Thr Leu Thr Leu Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg
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aac gtc acc cat ctg tac tca acc atc tta ggg cat cag att gga ctt
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Asn Val Thr His Leu Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu
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Ser Gly Arg Glu Ala His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro
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                                   -40
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Thr Ala Trp Ser Ser Asp Asp Cys Ala Leu His Gly His Cys Glu Gln
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gtg gta ttc aca gcc tgc atg acc ctc acg gcc agc cct ggg gtg ttc
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Val Val Phe Thr Ala Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe
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Pro Ser Leu Tyr Ser His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr
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Pro Arg Ser Gly Thr Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln
aat acg ccc aaa att aca atc ctt tct ggt gtt ata agg ggg cca ttg
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Asn Thr Pro Lys Ile Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu
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Glu Lys Ser Ile Met Leu
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Leu Arg Met
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Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly
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Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Ala Leu Phe
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Arg Leu Ser Pro Arg His Ile Pro Arg His Arg Gln Ala Val Asp Ser
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cag	Lev	v	gay	330	בננ	999	gat	ctg	gcc	CCC	ttc	LEC.	tat	gac	cag	824
Gln :	neu	Add	GIU	АТА		GIÀ	Asp	ьeu	Ala		Phe	Phe	Tyr	Asp		
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His	Gly	Gly	Glu	Val	Ile	Gly	Val	Leu	Trp	Lys	Pro	Thr	Ser	Phe	Gln	
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gaa cga gaa aaa aga agt atc agt gac agc gat gaa tta gct tca ggr Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly 10 15 20  Wtt ttt gtg ttc cct tac cca tat cca ttt cgc cca ctt cca cca att Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile 25 30 35  cca ttt cca aga ttt cca tgg ttt aga cgt aat ttt cct att cca ata Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Asn Phe Pro Ile Pro Ile 40 45 50 55  cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys 60 65	257 305 354

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Met Thr Cys Arg Gly Ser	
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tgc agc tac gct acc agg aga tct cca agc gaa ctc agc ctc cca Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro	101
-20 -15 -10	
age tee etg tgg gte eta gee aca age tet eea aca att act att gea	209
Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala	
-5 1 5	
ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt cca tca tca tkt cgt	257
Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg	
10 15 20 25	302
crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu	302
30 35 40	
tagetgecae tgaaaaraag geggtgaete cageteetee cataaagagg tgggagetgt	362
cctcggacca gccttacctg tgacactgca ccctcacggc cacccgacta ctttgcctcc	422
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Met Val Pro Trp Pro	
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agg ggc aag gtg aaa act gct cct att ccc atc tct agg ttt cct ttc	223
Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile Ser Arg Phe Pro Phe	
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ctc cct acc cac gac cca ccc acc cca gca cat tgg tct cca gca tct	271
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser -35 -25 -20	
cat cag cag ttt aaa cat kkg tca ccc ctc ctc act ttg gcc ctg ctg	319
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu	
-15 -10 -5	
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa	367
Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	
1 5 10	
aaa gca aaa aaa tta cct tcc ttc tcc agc ctg ccc ctg aca ctc tgg	415

Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu Pro Leu Thr L 15 20 25	eu Trp
cca tta act cct caa ttt gct gag ctc act aca gtg gca caa a	aa aaa 463
Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr Val Ala Gln L	ys Lys
30 35 40	45
ttg agg tgg tcc ggg acc cta ggt tgg ggt cca gtt ccc agc t	gg gtt 511
Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro Val Pro Ser T	
50 55 6	0
caa ttt ttt tta ggg tgaatggagg garagttggg gactgaaaas cctt	caaara 566
Gln Phe Phe Leu Gly	
65	
caatgttatt acagcaktot cocottatoc aaaktttoot tttootgadt tt	cagttagc 626
tatggtcaac cgcttggaaa atakttgaac acagtacaat aaratatttt ga	ggctggga 686
ktggtggctc atgcctgtaa taatcccagg actttgtgar accaaktttg aa	
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atgcattgca tagttgatca agtcactctc tggcctaaaa ccttccttgg ct	
ccctcaggat aaagtetgga cccctcage atg get tgt gag act cat g	
Met Ala Cys Glu Thr His G	iy vai
-30 -25	201
ctt gte cet get cae ete tet ggt ete ate aet tge ett ett g	
Leu Val Pro Ala His Leu Ser Gly Leu Ile Thr Cys Leu Leu A	ia Pne
-20 -15 -10	ha aas - ^^^
tgg gtc cca gcc tcc tgt atc cag aga tgc agt ggc tct cca t	
Trp Val Pro Ala Ser Cys Ile Gln Arg Cys Ser Gly Ser Pro L	
-5 1 5	10
ctc tgattcctcc tttcttttgg tcacagagaa agggtacttt ctctgtcaa	a 382
Leu	
tctcaactta gacttgactt cctccaagga gctttggcta tactctctc cw	
accetggeat actacacara teactetggg eteacttgee tgeetaatgg te	
agtaaactgt aagctccttg agggcaagga ttgtgttgga atttttgtat ta	
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                                                                      120
ttttgttctc tgctatgctc aggacccaga tcaaaggagc tcagtaacta tttacaggcg
                                                                      180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tec
                                                                      232
                                   Met Ala Pro His Thr Ala Ser
                                       -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                      280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                -25
                                    -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
                               -5
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
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aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                      441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                     501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
                                                                     561
getteectan ecetgaette ceaageetta gteatcacce teteteccae ceagggetea
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<222> 50..631

<221> sig\_peptide

<222> 50..244

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<222> 801..812

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gca gac tca act gag aag tca gcc tct gcg gca ggc acc agg aat ctg Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr Arg Asn Leu -45 -40 -35	154					
cct ttt cag ttc tgt ctc cgg cag gct ttg agg atg aag gct gcg ggc Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys Ala Ala Gly -30 -25 -20 -15	202					
att ctg acc ctc att ggc tgc ctg gtc aca ggc gtc gag tcc aaa atc Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu Ser Lys Ile -10 -5	250					
tac act cgt tgc aaa ctg gca aaa ata ttc tcg agg gct ggc ctg gac Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala Gly Leu Asp 5 10	298					
aat cyg agg ggc ttc agc ctt gga aac tgg atc tgc atg gcg tat tat Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met Ala Tyr Tyr 20 25 30	346					
gag agc ggc tac aac acc aca gcc car acg gtc ctg gat gac ggc agc Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser 35 40 45 50	394					
atc gac tay ggc atc ttc caa atc aac agc ttc gcg tgg tgc aga cgc Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp Cys Arg Arg 55 60 65	442					
gga aag ctg aag gag aac aac cac tgc cay gtc gcc tgc tca gcc ttg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys Ser Ala Leu 70 75 80	490					
rtc act gat gac ctc aca gat gca att atc tgt gcc arg aaa att gtt Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa Lys Ile Val 85 90 95	538					
aaa gag aca caa gga atg aac tat tgg caa ggc tgg aag aaa cay tgt Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys Lys His Cys 100 105 110	586					
gag ggg aga gac ctg tcc gas tgg aaa aaa ggc tgt gag gtt tcc Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu Val Ser 115 120 125	631					
taaactggaa ctggacccag gatgctttgc ascaacgccc tagggtttgc agtgaatgtc	691					
caaatgcctg tgtcatcttg tcccgtttcc tcccaatatt ccttctcaaa cttggagagg	751					
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<213> Homo sapiens

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ctggaaccaa cgggcacagt tggcaacacc atc atg aca tca caa cct gtt ccc Met Thr Ser Gln Pro Val Pro -65	174		
aat gag acc atc ata gtg ctc cca tca aat gtc atc aac ttc tcc caa	222		
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln -60 -55 -50			
gca gag aaa ccc gaa ccc acc aac cag ggg cag gat agc ctg aag aaa	270		
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly Gln Asp Ser Leu Lys Lys -45 -40 -35			
cat cta cac gca gar rtc aaa gtt att ggg act atc cag atc ttg tgt	318		
His Leu His Ala Glu Xaa Lys Val Ile Gly Thr Ile Gln Ile Leu Cys			
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Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe	300		
-10 -5 1			
tot oca aat tit ace caa gig act tot aca oig tig aac tot got tac	414		
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr 5 10 15			
cca ttc ata gga ccc ttt ttt ttt atc atc tct ggc tct cta tca atc	462		
Pro Phe Ile Gly Pro Phe Phe Ile Ile Ser Gly Ser Leu Ser Ile 20 25 30			
gcc aca aaa aaa agg tta acc aac ctt ttg gtg cat acc acc ctg gtt	510		
Ala Thr Lys Lys Arg Leu Thr Asn Leu Leu Val His Thr Thr Leu Val			
35 40 45 50	550		
gga age att etg agt get etg tet gee etg ggg ggt tte att aye etg	558		
Gly Ser Ile Leu Ser Ala Leu Ser Ala Leu Val Gly Phe Ile Xaa Leu 55 60 65	606		
tet gte aaa cag gee ace tta aat eet gee tea etg cak tgt gag ttg	606		
Ser Val Lys Gln Ala Thr Leu Asn Pro Ala Ser Leu Xaa Cys Glu Leu 70 75 80			
gmc aaa aat aat ata cca aca ara akt tat gtt yct tac ttt tat cat	654		
Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa Tyr Val Xaa Tyr Phe Tyr His 85 90 95	700		
gat toa ctt tat acc acg gac kgc tat aca gcc aaa gcc akt ctg gct	702		
Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr Thr Ala Lys Ala Xaa Leu Ala 100 105 110	750		
gga act ctc tct ctg atg ctg att tgc act ctg ctg gaa ttc tgc cwa	750		
Gly Thr Leu Ser Leu Met Leu Ile Cys Thr Leu Leu Glu Phe Cys Xaa 115 120 125 130			
set gtg etc act get gtg etg egg tgg aaa eag get tae tet gae tte	798		
Xaa Val Leu Thr Ala Val Leu Arg Trp Lys Gln Ala Tyr Ser Asp Phe			
135 140 145			
cct ggg agt gta ctt ttc ctg cct cam agt tac att ggw aat tct ggm	846		
Pro Gly Ser Val Leu Phe Leu Pro Xaa Ser Tyr Ile Gly Asn Ser Gly 150 155 160			
atg tcc tca aaa atg acy cat gac tgt gga tat gaa gaa cta ttg act	894		
Met Ser Ser Lys Met Thr His Asp Cys Gly Tyr Glu Glu Leu Thr 165 170 175			
tct taagaaaaaa gggagaaata ttaatcagaa agttgattct tatgataata Ser	947		
tggaaaagtt aaccattata gaaaagcaaa gcttgagttt cctaaatgta agcttttaaa	1007		
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<222> 395..400
<221> polyA site
<222> 433..444
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gtgtcggacc tctagagcta atctcactag atgtgagcca ttgtttatat tctagccatc
                                                                 120
ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                         Met Gln Val Pro His Leu Arg Val Trp
                              -35
                                                                 220
aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg Asn Leu Gly Phe Thr
      -25
                          -20
agt atg tgc ata ttg ttc cac tgt ctt ctt agc ttt cag gtt ttc aaa
                                                                 268
Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
                      -5
                                                                 322
aag aaa aga aaa ctt ara ctt ttc tgatgttctt ttttacgtaa ataaccattt
Lys Lys Arg Lys Leu Xaa Leu Phe
              10
                                                                 382
tattgttgtt ttgctttttc tgccttcaaa ctactcccac aggccaaata tavctggctg
                                                                 442
444
aa
<210> 297
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<221> polyA site
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ggc gag cat ccs rva btg tgaatkkkga cttttttctc ckccatttga Gly Glu His Pro Xaa Xaa 100 105	441
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10 15 20						
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Pro Glu Gly Val Ala Asp Leu Thr Gln Ile Asp Val Asn Val Gln Asp						
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His Phe Trp Asp Gly Lys Gly Cys Glu Met Ile Cys Tyr Cys Asn Phe						
40 45 50						
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Lys Arg Ile Ala Leu Leu Pro Lys Arg Arg Phe Leu Trp Thr Lys Asp						
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too ogt ggo tto occ otg ogo oto oag gco aco gag gto ogt ato tgo Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile Cys 5 10 15	154
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gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 40 45 50	250
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Phe Leu Leu Arg Phe Phe Ile Phe Cys Ser Leu Asn Thr Leu Leu Leu
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Gly Gly Val Asn Lys Ile Ala Glu Lys Ile Cys Gly Asp Leu Lys Asp
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Pro Cys Lys Leu Asp Met Asn Phe Gly Ser Cys Tyr Glu Val His Phe
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aga tat ttc tac aac aga acc tcc aaa aga tgt gaa act ttt gtc ttc
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Arg Tyr Phe Tyr Asn Arg Thr Ser Lys Arg Cys Glu Thr Phe Val Phe
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Glu Val Xaa Cys Val Ala Lys Tyr Lys Pro Pro Arg
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Gln Arg Phe Phe Ala Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr 20 cg cgt ctc cgt gca acc cac ggc tgc cgg aat ccc aca cca ctc gtc cag 245 Cys Arg Leu Arg Ala Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln 45 cg gac acc cac ggc tta gtc cc gat ggt gct gtc tgc 293 Leu Asp Gln Tyr Glu Asn His Gly Leu Val Pro Asp Gly Ala Val Cys 55 ccc acc ctc acc ctc acc gtc tac for 70 c 75 c 80 cag ttc acc 341 Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr 70 c 75 c 80 cag ttc acc 341 Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr 80 cag ttc acc 389 ttc acc acc tac cgt tgc tac tac tat gcc aca tac cgt tac tac tac gcc aca gag at a gag gtc ctg tgc tgc tgc tgc tgc tgc tgc tg	Ser Thr Gln	_	hr Pro Gly	-	Ser Pro Thr G	
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tggataagaa gtccactcac agaaatcctg aagatgccag ggctggcaaa tatgaaggta	180
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cagtgacgtc tttttcttca g atg atc cta tgt ttc ctt ctt cct cat cat  Met Ile Leu Cys Phe Leu Leu Pro His His  -15 -10	291
cgt ctt cag gaa gcc aga cag att caa gta ttg aag atg ctt cca agg Arg Leu Gln Glu Ala Arg Gln Ile Gln Val Leu Lys Met Leu Pro Arg -5 10	339
gaa aaa tta aga aga aga gaa gag aga aaa caa ata aat ggg aaa aaa Glu Lys Leu Arg Arg Arg Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys 15 20 25	387
raa agg aca aaa tat gaa aca cca aga aaa rga raa gga aaa aaa gga Xaa Arg Thr Lys Tyr Glu Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly 30 40	435
gga aac mac cmc wtw tkt cmc ctt tcc aar agg gac tgaaactggg Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp 45 50	481
ctgacccttt tgatttccaa vetcasegtt ttggtgtaag geggeeaaar aaggatgegg aseceageae tgtgaageet acaaaaacat tgatgegetg gettggggat ttgaatttga acatetttca caetaagtte agaeteatga aaccaatett cagatgetet gtaaaccaca taataaagag tttggaaatt aaaaaaaaar aa	541 601 661 693
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-30 -25 aga gtg agc tcg gtg gga gcg aat ktc cta tgc ctg ggg atg gcc ctg Arg Val Ser Ser Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu -20 -15 -10	157

tat																
Lyc	ccg	cgt	caa	gca	acg	cgc	atc	ccg	ctc	aac	ggc	acc	tgg	ctc	ttc	205
-	Pro	Arg	Gln	Ala	_	Arg	Ile	Pro		Asn	Gly	Thr	Trp		Phe	
-5					1				5				- 4- 4-	10		253
acc	ccc	gtg	agc	aag	atg	gcg	act	gtg	aar	agt	gag	CCC	att	gag	egt.	253
Thr	Pro	Val		Lys	Met	Ala	Thr		Lys	Ser	GIU	Leu		GIU	Arg	
			15					20					25			201
ttc	act	tcc	gar	aag	CCC	gtt	cat	cac	agt	aag	gtc	tcc	atc	ata	gga	301
Phe	Thr	Ser	Glu	Lys	Pro	Val		His	Ser	Lys	Val		He	lle	GIA	
		30					35					40				
act	gga	tcg	gtg	ggc	atg	gcc	tgc	gct	atc	agc	atc	tta	tta	aaa	ggc	349
Thr	Gly	Ser	Val	Gly	Met	Ala	Cys	Ala	Ile	Ser	Ile	Leu	Leu	Lys	СΙΆ	
	45					50					55					
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Leu	Ser	Asp	Glu	Leu	Ala	Leu	Val	Asp	Leu		Glu	Xaa	Lys	Leu		
60					65					70					75	
				gat												445
Gly	Glu	Thr	Met	Asp	Leu	Gln	His	Gly	Ser	Pro	Phe	Thr	Lys	Met	Pro	
				80					85					90		
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Asn	Ile	Val	Cys	Ser	Lys	Xaa	Tyr	Phe	Val	Thr	Ala	Asn	Ser	Asn	Leu	
			95					100					105			
gtg	att	atc	aca	gca	ggt	gca	cgc	caa	raa	aag	gga	gaa	acg	cgc	ctt	541
Val	Ile	Ile	Thr	Ala	Gly	Ala	Arg	Gln	Xaa	Lys	Gly	Glu	Thr	Arg	Leu	
		110					115					120				
aat	tta	stc	cag	cga	aat	gtg	gcc	atc	ttc	aag	tta	atg	att	tcc	agt	589
Asn	Leu	Xaa	Gln	Arg	Asn	Val	Ala	Ile	Phe	Lys	Leu	Met	Ile	Ser	Ser	
	125					130					135					
att	gtc	cag	tac	agc	ccc	cac	tgc	aaa	ctg	att	att	gtt	tcc	aat	cca	637
Ile	Val	Gln	Tyr	Ser	Pro	His	Cys	Lys	Leu	Ile	Ile	Val	Ser	Asn	Pro	
140					145					150					155	
gtg	gat	atc	tta	act	tat	gta	gct	tgg	aag	ttg	agt	gca	ttt	ccc	aaa	685
Val	Asp	Ile	Leu	Thr	Tyr	Val	Ala	Trp	Lys	Leu	Ser	Ala	Phe	Pro	Lys	
				160	_				165					170		
aac	cgt	att	att	gga	agc	ggc	tgt	aat	165 ctg	ata	mhg	gct	cgt	170 ttt	cgt	733
aac Asn	cgt Arg	att Ile	att Ile		agc	ggc	tgt	aat	165 ctg	ata	mhg	gct	cgt	170 ttt	cgt	733
Asn	Arg	Ile	Ile 175	gga Gly	agc Ser	ggc Gly	tgt Cys	aat Asn 180	165 ctg Leu	ata Ile	mhg Xaa	gct Ala	cgt Arg 185	170 ttt Phe	cgt Arg	733
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Asn ttc Phe tgg Trp gtg Val 220 act	ttg Leu atc Ile 205 aac Asn	Ile att Ile 190 ctc Leu ata Ile aaa	Ile 175 gga Gly gga Gly gct Ala	gga Gly caa Gln gag Glu ggt Gly cct	agc Ser aag Lys cat His gtc Val 225 gag	ggc Gly ctt Leu gga Gly 210 cct Pro	tgt Cys ggt Gly 195 gac Asp ttg Leu	aat Asn 180 atc Ile tca Ser aag Lys	165 ctg Leu cat His agt Ser gat Asp	ata Ile tct Ser gtt Val ctg Leu 230 gtc	mhg Xaa gaa Glu cct Pro 215 aac Asn	gct Ala agc ser 200 gtg Val tct ser	cgt Arg 185 tgc Cys tgg Trp gat Asp	170 ttt Phe cat His agt Ser ata Ile	cgt Arg gga Gly gga Gly gga Gly 235 act	781 829 877
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Asn ttc Phe tgg Trp gtg Val 220 act Thr gca Ala att Ile agg Arg	Arg ttg Leu atc Ile 205 aac Asn gat Asp act Thr ggc Gly aga Arg 285 gaa	Ile att Ile 190 ctc Leu ata Ile aaa Lys gcc Ala cta Leu 270 ata Ile gaa	Ile 175 gga Gly gct Ala gat Asp tat Tyr 255 tct Ser cat His	gga Gly caa Gln gag Glu ggt Gly cct Pro 240 gag Glu gtg Val cca Pro	agc Ser aag Lys cat His gtc Val 225 gag Glu att Ile gcc Ala gtt Val	ggc Gly ctt Leu gga Gly 210 cct Pro caa Gln att Ile gat Asp tcc Ser 290 agt	tgt Cys ggt Gly 195 gac Asp ttg Leu tgg Trp aaa Lys tta Leu 275 acc Thr	aat Asn 180 atc Ile tca Ser aag Lys atg Met 260 aca Thr ata Ile cct	165 ctg Leu cat His agt Ser gat Asp aat Lys gaa Lys gaa Glu act Thr	ata Ile tct Ser gtt Val ctg Leu 230 gtc Val ggt Gly agt Ser aag Lys	mhg Xaa gaa Glu cct Pro 215 aac Asn cac His tat Tyr att Ile ggc Gly 295 ctg	gct Ala agc Ser 200 gtg Val tct Ser aaa Lys act Thr ttg Leu 280 ctc Leu	cgt Arg 185 tgc Cys tgg Trp gat Asp gaa Glu tct 265 aag Lys tat Tyr	170 ttt Phe cat His agt Ser ata Ile gtg Val 250 tgg Trp aat Asn gga Gly aac	cgt Arg gga Gly gga Gly 235 act Thr gcc Ala ctt Leu ata Ile	781 829 877 925 973 1021
Asn ttc Phe tgg Trp gtg Val 220 act Thr gca Ala att Ile agg Arg rat Xaa	Arg ttg Leu atc Ile 205 aac Asn gat Asp act Thr ggc Gly aga Arg 285 gaa	Ile att Ile 190 ctc Leu ata Ile aaa Lys gcc Ala cta Leu 270 ata Ile gaa	Ile 175 gga Gly gct Ala gat Asp tat Tyr 255 tct Ser cat His	gga Gly caa Gln gag Glu ggt Pro 240 gag Glu gtg Val	agc Ser aag Lys cat His gtc Val 225 gag Glu att Ile gcc Ala gtt Val	ggc Gly ctt Leu gga Gly 210 cct Pro caa Gln att Ile gat Asp tcc Ser 290 agt	tgt Cys ggt Gly 195 gac Asp ttg Leu tgg Trp aaa Lys tta Leu 275 acc Thr	aat Asn 180 atc Ile tca Ser aag Lys atg Met 260 aca Thr ata Ile cct	165 ctg Leu cat His agt Ser gat Asp aat Lys gaa Clu act Thr	ata Ile tct Ser gtt Val ctg Leu 230 gtc Val ggt Gly agt Ser aag Lys	mhg Xaa gaa Glu cct Pro 215 aac Asn cac His tat Tyr att Ile ggc Gly 295 ctg	gct Ala agc Ser 200 gtg Val tct Ser aaa Lys act Thr ttg Leu 280 ctc Leu	cgt Arg 185 tgc Cys tgg Trp gat Asp gaa Glu tct 265 aag Lys tat Tyr	170 ttt Phe cat His agt Ser ata Ile gtg Val 250 tgg Trp aat Asn gga Gly aac	cgt Arg gga Gly gga Gly 235 act Thr gcc Ala ctt Leu ata Ile	781 829 877 925 973 1021
Asn ttc Phe tgg Trp gtg Val 220 act Thr gca Ala att Ile agg Arg rat Xaa 300	ttg Leu atc Ile 205 aac Asn gat Asp act Thr ggc Gly aga Arg 285 gaa Glu	Ile att Ile 190 ctc Leu ata Ile aaa Lys gcc Ala cta Leu 270 ata Ile gaa Glu	Ile 175 gga Gly gct Ala gat Asp tat Tyr 255 tct Ser cat His gta Val	gga Gly caa Gln gag Glu ggt Gly cct Pro 240 gag Glu gtg Val cca Pro	agc Ser aag Lys cat His gtc Val 225 gag Glu att Ile gcc Ala gtt Val ctc Leu 305	ggc Gly ctt Leu gga Gly 210 cct Pro caa Gln att Ile gat Asp tcc Ser 290 agt Ser	tgt Cys ggt Gly 195 gac Asp ttg Leu tgg Trp aaa Lys tta Leu 275 acc Thr	aat Asn 180 atc Ile tca Ser aag Lys atg Met 260 aca Thr ata Ile cct Pro	165 ctg Leu cat His agt Ser gat Asp aat Lys gaa Glu act Thr tgt Cys	ata Ile tct Ser gtt Val ctg Leu 230 gtc Val ggt Gly agt Ser aag Lys atc Ile 310	mhg Xaa gaa Glu cct Pro 215 aac Asn cac His tat Tyr att Ile ggc Gly 295 ctg Leu	gct Ala agc Ser 200 gtg Val tct Ser aaa Lys act Thr ttg Leu 280 ctc Leu	cgt Arg 185 tgc Cys tgg Trp gat Asp gaa Glu tct Ser 265 aag Lys tat Tyr gag Glu	170 ttt Phe cat His agt Ser ata Ile gtg Val 250 tgg Trp aat Asn gga Gly ac	cgt Arg gga Gly gga Gly 235 act Thr gcc Ala ctt Leu ata Ile ggt Gly 315	781 829 877 925 973 1021
Asn ttc Phe tgg Trp gtg Val 220 act Thr gca Ala att Ile agg Arg rat Xaa 300 att	Arg ttg Leu atc Ile 205 aac Asn gat Asp act Thr ggc Gly aga Arg 285 gaa Glu acc	Ile att Ile 190 ctc Leu ata Ile aaa Lys gcc Ala cta Leu 270 ata Ile gaa Glu aac	Ile 175 gga Gly gct Ala gat Asp tat Tyr 255 tct Ser cat His gta Val	gga Gly caa Gln gag Glu ggt Gly cct Pro 240 gag Glu gtg Val cca Pro	agc Ser aag Lys cat His gtc Val 225 gag Glu att Ile gcc Ala gtt Val ctc 1305 aag	ggc Gly ctt Leu gga Gly 210 cct Pro caa Gln att Ile gat Asp tcc Ser 290 agt Ser ata	tgt Cys ggt Gly 195 gac Asp ttg Leu tgg Trp aaa Lys tta 275 acc Thr	aat Asn 180 atc Ile tca Ser aag Lys atg Met 260 aca Thr ata Ile cct Pro	165 ctg Leu cat His agt Ser gat Asp aat Lys gaa Lys gaa Clu act Thr tgt Cys acc	ata Ile tct Ser gtt Val ctg Leu 230 gtc Val ggt Gly agt Ser aag Lys atc Ile 310 ct	mhg Xaa gaa Glu cct Pro 215 aac Asn cac His tat Tyr att Ile ggc 295 ctg Leu gaa	gct Ala agc Ser 200 gtg Val tct Ser aaa Lys act Thr ttg Leu 280 ctc Leu gga Gly	cgt Arg 185 tgc Cys tgg Trp gat Asp gaa Glu tct 265 aag Lys tat Tyr gag Glu gag	170 ttt Phe cat His agt Ser ata Ile gtg Val 250 tgg Trp aat Asn gga Gly ac Asn	cgt Arg gga Gly gga Gly 235 act Thr gcc Ala ctt Leu ata Ile ggt Gly 315 cat	781 829 877 925 973 1021 1069

330

320 325

320 325 330	
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335 340 345 ctt taaagttgcc taaaactacc attccgaaat tattgaagag atcatagata	1266
Leu	
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tgtgttctag aaattccgac tcttttcatt agatatatgc tatttctttc attcttgctg	1566
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Met Val Cys Leu Phe Phe Arg Leu Ile Phe Ser Glu His Leu Pro Ile	
-10 -5 1 5	
ata ggc act gtc act tct cac aaa act ggg aca cta act gtt tat cca	152
Ile Gly Thr Val Thr Ser His Lys Thr Gly Thr Leu Thr Val Tyr Pro	
10 15 20	
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Thr Ser Ala Gly	
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gctgcaggaa gtaagaaaga agaaaaaagg agtgataaag ataaaaaaaa	384
gtccttccac caaaacccat taatttccat atcatcatct gcataararg gaaaattcct	444
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aac atg ccc acc act ggc ccc aac agc ctg agt tat gct agc tct gcc Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala -20 -15 -10	277
ctg tcc ccc tgt ctg acc gct cca aag tcc ccc cga ctt gct atg atg Leu Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met -5 5 10	325
cct gac aac taaatatcct tatccaaatc aataaarwra raatcctccc Pro Asp Asn	374 405
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Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg	
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-10 -5 1  ggc agc cac tgg aca gag aga cca akt cag akt tca ccg tgg akt tct  Gly Ser His Trp Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser	326
5 10 15 ctg tca gcg acc acc agg ggg tgatcacacg gaaggtgaac atccaggtcg Leu Ser Ala Thr Thr Arg Gly	377
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ccc gca agg cgg cat ctg ctg gtc ctg ctg ctc ctc tct acc ctg Pro Ala Arg Arg His Leu Leu Val Leu Leu Leu Leu Ser Thr Leu -20 -15 -10	161
gtg atc ccc tcc gct gca gct cct atc cat gat gct gac gcc caa gag Val Ile Pro Ser Ala Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu -5 1 5 10	209
agc tcc ttg ggt ctc aca ggc ctc cag agc cta ctc caa ggc ttc agc Ser Ser Leu Gly Leu Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser 15 20 25	257
cga ctt ttc ctg aaa ggt aac ctg ctt cgg ggc ata gac agc tta ttc	305

720	Leu	Dha	T.au	Lare	Glv	λεη	Len	Len	Δτα	Glv	Tle	Asp	Ser	Leu	Phe	
Arg	Dea	FIIC	30	БуЗ	Cry	AUII	Leu	35		O. J			40			
tct	gcc	CCC	atg	gac	ttc	cgg	ggc	ctc	cct	999	aac	tac	cac	aaa	gag	353
Ser	Ala	Pro	Met	Asp	Phe	Arg	Gly	Leu	Pro	Gly	Asn	Tyr	His	Lys	Glu	
		45					50					55				
gag	aac	cag	gag	cac	cag	ctg	999	aac	aac	acc	ctc	tcc	agc	cac	ctc	401
	Asn															
	60					65					70					
cag	atc	gac	aag	atg	acc	gac	aac	aag	aca	gga	gag	gtg	ctg	atc	tcc	449
	Ile															
75		•	•		80	_		-		85					90	
gag	aat	qtq	ata	qca	tcc	att	caa	cca	vcg	gag	999	anc	ttc	gag	ggt	497
	Asn															
				95					100		_			105	-	
gat	ttg	aaq	ath	ccc	agg	atq	qaq	gar	aag	gag	gcc	ctg	gta	ccc	mtc	545
Asp	Leu	Lvs	Val	Pro	Arg	Met	Glu	Glu	Lys	Glu	Āla	Leu	Val	Pro	Xaa	
		_	110					115	•				120			
car	aag			gac	agc	ttc	cac	aca	gaa	ctc	cat	ccc	cgg	gtg	gcc	593
Gln	Lys	Ala	Thr	Asp	Ser	Phe	His	Thr	Glu	Leu	His	Pro	Arg	Val	Ala	
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	Trp															
	140			-1-		145	3				150		•			
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	Gly															
155	011	017			160			-1-	3	165	3				170	
	gat	gga	ctc	cac		aaa	acc	cac	aaq	gac	rtc	cta	daa	raq	ggg	737
Ara	Asp	Glv	Len	Ara	Lvs	Glv	Thr	His	Lvs	Asp	Xaa	Leu	Xaa	Xaa	Gly	
1119	p	<b>U</b> -7		175	-1-	<b>-</b> -,			180	<u>F</u>				185	•	
acc	gar	age	tcc		cac	too	agg	cta	tcc	ccc	cga	aar	amm	cac	tta	785
	Glu															
****	<b>01</b> u		190		****	501	5	195			5	-1-	200			
cta	tac	atc		ard	ccc	tct	caa		cta	tard	aata	aaa d		aaaa	ar	835
	Tyr			_				_	_		9999	933 :	,	٠٠٠٠٠		
Deu	- Y -	205	Dea	Aaa	210	JUL	210		u							
mac	ctac		t acco		at c	arace			raaco	racc	atai	. aaaa	at a	aaagt	tcttt	895
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aar gca gct ggg cag atc cag gcc tgg tgg cgt ggg gtc ctg gtg cgc Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu Val Arg -25 -20 -15	201
agg acc ctg ctg gtt gct gcc ctc agg gcc tgg atg att cag tgc tgg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln Cys Trp -10 -5 1 5	249
tgg agg acg ttg gtg cag aga cgg atc cgt cag cgg cgg cag gcc ctg Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln Ala Leu  10 15 20	297
ttr ggg gtc tac gtc atc cag gag cag gcg gtc aag ctc cag tcc Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu Gln Ser 25 30	345
tgc atc cgc atg tgg cag tgc cgg caa tgt tac cgc caa atg tgc aat Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met Cys Asn 40 45	393
gct ctc tgc ttg ttc cag gtc cca aaa agc agc ctt gcc ttc caa act Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe Gln Thr 55 60 65 70	441
gat ggc ttt tta cag gtc caa tat gca atc cct tca aag cag cca gag Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln Pro Glu 75 80 85	489
ttc cac att gaa atc cta tca atc tgaaaggcct ggggcatgga gaacaggctg Phe His Ile Glu Ile Leu Ser Ile 90	543
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				-55	gat				-50					-45		273
			-40		Asp			-35	_				-30			
Arg	Ser	His -25	Ala	Asp	caa Gln	Asp	Ser -20	Asn	Pro	Lys	Ala	Glu -15	Ala	Leu	Leu	321
					tgc Cys											369
					cca Pro											417
_	_			ccc	ccs Pro	-	tgaa	accad		gtct	ccta	at co	ettte	ggcca	ı	468
			agga												accata ggagct	528 588
gcag	gaat	ca ç	ggtgo	cagag		ggaaa	atgga	act	aac	ctca	ggaa	ıggt	gt a		acagag	648 697
<b>J</b>			•	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	,		_				_					
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cta	ctc	acc	tgg	ctt	ttc	aca	cta		25 ttc	ttg	atc	atg	_	20 gtg	ttg	222
Leu	Leu	Thr -15	Trp	Leu	Phe	Thr	Leu -10	Leu	Phe	Leu	Ile	Met -5	Leu	Val	Leu	
		gat			gca Ala		tgg									270
-	1	_		_	5 act		_		_	10					15	318
					Thr											310

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tactacttcc ataaaacagg attggtgaat cacggacttc	
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3 3 13 3 2	Met
atc cct ctg ata age cac ctt gcc gag gct gct	cct cct acc tca tqq 225
Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala	
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ago ott ata toa agt gtg otg aat gtg ggo cac	ctc ctt ttt tcc tct 273
Ser Leu Ile Ser Ser Val Leu Asn Val Gly His	
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1 5 10	15
atc ata ctt atg aaa taatggcttc agattttcct g	tccttgatc ccagctggac 376
Ile Ile Leu Met Lys	
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ggatgtagcc aatcaaatgt gcaccaarac caaggaggag	
gcatttcatc aataacccyc tgtttgcatc trscctgctg	
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ctttgactcc ttgctttctc gggacatggc cgggtacwtg	
tgaggaattt gacaattatg cagaatggga cttgagagac	
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gtggagatgt gctgaggtct tctccctgat cgtcttctcc tccctgctga ccgacggcta
                                                                      180
ccagaackag atg gag tot ccg cag ctc cac tgc att ctc aac agc aac
                                                                      229
          Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn
                       -35
                                           -30
age gtg gee tge age ttt gee gtg gga gee gge tte etg gee tte etc
                                                                      277
Ser Val Ala Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu
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                   -20
age tge etg gee tte ete gte etg gae aca eag gag ace ege att gee
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Ser Cys Leu Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala
ggc acc cgc ttc aag aca gcc ttc cag ctc ctg gac ttc atc ctg gct
                                                                      373
Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
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                           15
gtt ctc tgg gca gtt gtc tgg ttc atg ggt ttc tgc ttc ctg gcc aac
                                                                      421
Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
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                                            35
caa tgg cag cat tcg ccg ccc aaa gar kkc ctc ctg ggg agc agc agt
                                                                      469
Gln Trp Gln His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser
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                                        50
gcc cag gca gcc atc ggc stt cac ctt ctt ctc cat cct tgt ctg gat
                                                                      517
Ala Gln Ala Ala Ile Gly Xaa His Leu Leu Leu His Pro Cys Leu Asp
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                                    65
att cca rgc cta cct ggc akk cca gga cct ccg aaa tgatgctcca
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Ile Pro Xaa Leu Pro Gly Xaa Pro Gly Pro Pro Lys
gtcccttacm arcgcttcct ggatgaaggt ggcatggtgs kkaacaccct ccccttgccc
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<213> Homo sapiens

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ggt tta ttt cat ttt cct aca cca ctg acc cga ata tgc ccg gcg cca Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile Cys Pro Ala Pro -30 -25 -20	165
tgg gga ctc cgg ctt tgg gag aag ctg acg ttg tta tcc cca gga ata Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu Ser Pro Gly Ile -15 -10 -5	213
gct gtc act ceg gtc cag atg gca ggc aag aag gac tac cct gca ctg Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp Tyr Pro Ala Leu  1 5 10 15	261
ctt tcc ttg gat gag aat gaa ctc gaa gag cag ttt gtg aaa gga cac Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe Val Lys Gly His 20 25 30	309
ggt cca ggg ggc cag gca acc aac aaa acc agc aac tgc gtg gtg ctg Gly Pro Gly Gln Ala Thr Asn Lys Thr Ser Asn Cys Val Val Leu 35 40 45	357
aar mac atc ccc tca ggc atc gtt gta aag tgc cat cag aca aga tca Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His Gln Thr Arg Ser 50 60	405
gtt gat cag aac aga aag cta gct cgg aaa atc cta caa gag aaa gta Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu Gln Glu Lys Val 65 70 75	453
rat gtt ttc tac aat ggt gaa aac agt cct gtt cac aaa gaa aaa cga Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His Lys Glu Lys Arg 80 85 90 95	501
gaa gcg gcg aag aaa aaa car gaa agg aaa aaa aga gca aag gaa acc Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg Ala Lys Glu Thr 100 105 110	549
ctg gaa aaa aag aas ctm ctt aaa raa ctg tgg gag tca agt aaa aag Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu Ser Ser Lys Lys 115 120 125	597
gtc cac tgagaaaaga attagagatt ccaactgaca gaatctgcca gaagctccca Val His	653
gggaataatg gtggcgagtt ccatcaccag cattattata gtgcttcaaa agaaatattt	713
ttgatgaact taaaagacaa caaatttatt taaatggtgc actaaactgt agtgaacaga	773
gacatgcacg attcaagaat aaaactcggc cgggcacggt ggacggtgcc tcacatctgt	833
aatcccagca ctttgggagg ccgaggcggg cggatcactt gaggtcagga gtttgagacc	893
agcctggcca acatggtgaa accccgtctc tactaaaaat acaaaaaatt agccaggcat	953
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ctgggaggcg gaggttgcag tgagctgaga tcgcgccact gcactcaagc ctgggcaaca	1073
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Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly Leu Val Thr
            -20
                                -15
ctg ctc ggc ctg gct gtg ggc tcc tac ttg gtt cgg agg tcc cgc cgg
                                                                      151
Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg Ser Arg Arg
       - 5
                                                                      199
cct cag gtc act ctc ctg gac ccc aat gaa aag tac ctg cta cga ctg
Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu Leu Arg Leu
                                        20
                    15
cta gac aag acg act gtg agc cac aac acc aag agg ttc cgc ttt gcc
                                                                      247
Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe Arg Phe Ala
                30
                                   35
                                                                      295
ctg ccc acc gcc cac cac act ctg ggg ctg cct gtg ggc aaa cat atc
Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly Lys His Ile
                                50
                                                    55
                                                                      343
tac etc tec acm mga att gat ggc age etg gtc atc agg eca tac act
Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg Pro Tyr Thr
                           65
                                                70
                                                                      391
cct gtc acc agt gat gag gat caa ggc tat gtg gat ctt gtc mtc aag
Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu Val Xaa Lys
                        80
                                            85
                                                                      439
gtc tac ctg aag ggt gtg cac ccc aaa ttt cct gag gga ggg aar atg.
Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly Gly Lys Met
                    95
                                        100
                                                                      487
tot cak tac ctg gat asc ctg aaa gtt ggg gat btg gtg gaa ttt csg
Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val Glu Phe Xaa
                110
                                    115
                                                                      535
ggg cca agc ggg ttg ctc act tac act gga aaa ggg cat ttt aac att
Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His Phe Asn Ile
                                130
            125
                                                                      583
cag ccc aac aag aat ctc cac cag aac ccc gag tgg cga aga aac tgg
Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg Arg Asn Trp
                            145
gaa tgattgccgg cgggacagga atcaccccaa tgctacagct gatccgggcc
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Glu
                                                                      696
atcctgaaag tccctgaaga tccaacccag tgctttctgc tttttgccaa ccagacagaa
aaggatatca tettgeggga ggaettagag gaactgeagg eeegetatee caategettt
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aagetetggt teactetgga teateeceea aaagettggg cetacageaa gggetttgtg
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actgccgacw tgatccggga acacctgccc gctccagggg atgatgtgct ggtactgctt
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936

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                                          Met Thr Pro Arg Ile Leu
                                                                     164
age gaa gte cag ttt tea gea ttt tgt eet tat tgg aca ata gea agg
Ser Glu Val Gln Phe Ser Ala Phe Cys Pro Tyr Trp Thr Ile Ala Arg
                                -50
            -55
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Ile Leu Glu Arg Val Gly Ser Ala Cys Phe Arg Leu Glu Leu Cys Ala
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gct att gtc gga tat ttt gtc tta gat gta cgt act ttc ctg ttc att
                                                                     260
Ala Ile Val Gly Tyr Phe Val Leu Asp Val Arg Thr Phe Leu Phe Ile
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gtg gta tgt gta att tgc gtt act ttg aat ttt cca cgt ttt tac ttt
                                                                     308
Val Val Cys Val Ile Cys Val Thr Leu Asn Phe Pro Arg Phe Tyr Phe
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Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly Thr Pro Pro Ile Gly Val
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cac att ccc tct ccc tararcacac tcccttggat ttcctcradt ggggtctgct
His Ile Pro Ser Pro
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gcggtgaagc tttcccattt tatgtgcaga ttattttcag agggtatata gaattcaggc
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Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa Leu Leu Leu Leu
                -15
                                    -10
                                                                      151
cta ata gcc ttg gag atc atg gtt ggt ggt cac tct ctt tgc ttc aac
Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser Leu Cys Phe Asn
                                                                      199
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Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro Trp Cys Glu Ala
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                                                                      247
His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr Asn Ser Asp Asn
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                                        40
aac atg gtc aaa cct ctg ggc ctc ctg ggg aag aag gta tat gcc acc
                                                                      295
Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys Val Tyr Ala Thr
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                50
age act tgg gga gaa ttg ace caa acg ctg gga gaa gtg ggg cga gac
                                                                      343
Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu Val Gly Arg Asp
                                70
ctc agg atg ctc ctt tgt gac atc aaa ccc car ata aag acc agt gat
                                                                      391
Leu Arg Met Leu Cys Asp Ile Lys Pro Gln Ile Lys Thr Ser Asp
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Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg Glu Ala Glu Arg
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                                                                      487
tgc act ggt gca tcc tgg cag ttc gcc acc aat gga gag aaa tcc ctc
Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly Glu Lys Ser Leu
                    115
                                                                      535
ctc ttt qac qca atq aac atg acc tgg aca gta att aat cat gaa gcc
Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile Asn His Glu Ala
                                    135
                                                                      583
agt wag atc aag gag aca tgg aag aaa gac aga ngg ctg gaa aak tat
Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa Leu Glu Xaa Tyr
                                150
                                                                      631
ttc agg aag ctc tca aar gga gac tgc gat cac tgg ctc agg gaa ttc
Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp Leu Arg Glu Phe
                           165
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tta ggg cac tgg gaa gca atg cca raa ccg ama gtg tcm cca rta aat
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Leu Gly His Trp Glu Ala Met Pro Xaa Pro	Xaa Val Ser Pro Xaa Asn 185
gct tca raw atc cac tgg tct tct tct art	cta cca raw ara tgg atc 727
Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa 190 195	Leu Pro Xaa Xaa Trp Ile 200 205
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Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu 210 215	
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Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser 225 230	Thr Xaa Xaa
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<pre>&lt;222&gt; 10061016  &lt;400&gt; 321 ac atg tgc cct agt ctg gaa gag gct ccc    Met Cys Pro Ser Leu Glu Glu Ala Pro</pre>	Ser Val Lys Gly Thr Leu -50  ttt gga gcc tca aac atc 95  Phe Gly Ala Ser Asn Ile -35 -30 gct cga ggt gca ccg gtc 143 Ala Arg Gly Ala Pro Val
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627

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ccttgtatga actggtctaa agactgttag tggggtgtta gttgattttt cctggtatac

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Met	Asn	Xaa	Tvr	Ala	Ser	Pro	Phe	Asn	Xaa	Gln	Leu	Xaa	Tyr	Leu	Xaa	
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Ser	TYL	-20	Giu	GIII	Olu	Deu	-15	p				-10				
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Cag	uic.	Cay	Val	Uie	λla	Val	Gln	Gln	Len	Δla	Lvs	Val	Met	Gly	Trp	
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GIn	vaı	ьец	Ser		Ser	ASII	urs	vai	20	пец	GIY	FIO	***	25	501	
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apt	ggt	aat	gca	CCL	gcc	atc	mba	gra	310	Dwa	Cla	7727	77-1	act	Met	5.10
Xaa	GIĀ	Asn		ser	Ата	TTE	Thr	35	Ald	PIO	GIII	vaı	40	Thr	Mec	
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cta	ttt	cag	ttc	gta	atg	gac	ctg	aaa	grg	gca	gca	aya	Ton	tgg	Dhe	374
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Lys	Ile	Thr	Asn	Gly		Ile	Phe	Val	Gly		Ser	гля	ьуs	Phe		
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Cys	Leu	His	Leu	Ala	Leu	Val	Tyr	Tyr	Asp	Phe	Phe	Gln	Met	Phe	Pro	
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Lys	His	Lys	Glu	Glu	Ile	Thr	Ser	Lys	Arg	Val	Leu	Phe	Leu	Lys	Ile	
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ata	att	agg	aaa	tqt	ttt	att	tage	cact	ttc a	aaac	tttt	ca c	ttta	taaa	t	733
				Cys			_									
155		_	. 4	• •	160											
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aaa	ataa	tat (	attt	ttca	ta c	agtt	taaa	a ta	ttac	taac	tta	agga	ttt	ctate	gtgctt	853
ttt	aaaa	tat	taat	tett	tora:	tatt	gaca	t ca	aata	aagt	ato	tgat	tta	aaaa	aaaaaa	913
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WO 99/31236 -248- PCT/IB98/02122 -

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                     -15
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ccc ctg cac ttt tct ga Pro Leu His Phe Ser As					210
aca ctt act acc aac ac Thr Leu Thr Thr Asn Th		aaa cat tct			258
atg mat ctg gta tta gg Met Xaa Leu Val Leu Gl 15	ga aaa tta d	_		agaaaaaaga	311
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				- 5					1				5			
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Ser	Ile	Ser	Glu	Leu	Cys	Lys	Gly	Gln	Glu	Leu	Glu		Ser	Gly	Ala	
		10					15					20				244
					cca											344
GIÀ		Thr	Val	Ala	Pro	Pro	GIn	Ala	vai	ser	Leu 35	GIn	GIY	116	lyr	
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PIO	105	261	PIO	TÀT	PIO	110	FIO	GIII	пец	Gry	115	1115	AI u	O±7	<b></b>	
atc		taad	caati	tta 1	tgcad		ta ct	tagti	tta	t tai		acca	ttc	caqqq	ata	640
_	Asn				- 5					3					-	
120																
gctt	tgaa	aaa a	aagta	atct	ca aa	aaag	gcaad	c ate	gggc	cgag	cgca	agtg	gct (	cacgo	cctgta	700
															agacca	760
															tgtggt	820
															aaccca	880
					-			g tgo	ccaci	tgcg	ctc	cago	ctg 9	ggcg	acagag	940
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<210> 337
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<211> 901

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 133..846

<221> sig\_peptide

<222> 133..345

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 seq VVSFLLLLAGLIA/TY

<221> polyA\_site

<222> 890..901

<400> 337

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aggaacrtca ta atg rwn nnk ttc aca gac ccc tct tca gtg aat gaa aag  Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys  -70  -65  -60	171
aag agg agg gag cgg gaa gaa agg cag aat att gtc ctg tgg aga cag Lys Arg Arg Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln -55 -50 -45	219
ccg ctc att acc ttg cag tat ttt tct ctg gaa atc ctt gta atc ttg	267

Pro	Leu	Ile	Thr	Leu	Gln	Tyr	Phe	Ser	Leu	Glu	Ile	Leu -30	Val	Ile	Leu	
aag Lys	gaa Glu -25	tgg Trp	acc Thr	tca Ser	aaa Lys	tta Leu -20	tgg Trp	cat His	cgt Arg	caa Gln	agc Ser -15	att Ile	gtg Val	gtg Val	tct Ser	315
ttt Phe -10	tta	ctg Leu	ctg Leu	ctt Leu	gct Ala -5	ggg Gly	ctt Leu	ata Ile	gct Ala	acg Thr 1	tat Tyr	tat Tyr	gtt Val	gaa Glu 5	gga Gly	363
gtg	cat His	caa Gln	cag Gln 10	tat Tyr	gtg Val	caa Gln	cgt Arg	ata Ile 15	gag Glu	aaa Lys	cag Gln	ttt Phe	ctt Leu 20	ttg Leu	tat Tyr	411
gcc Ala	tac Tyr	tgg Trp 25	ata Ile	ggc Gly	tta Leu	gga Gly	att Ile 30	ttg Leu	tct Ser	tct Ser	gtt Val	999 Gly 35	ctt Leu	gga Gly	aca Thr	459
Gly 999	ctg Leu 40	cac His	acc Thr	ttt Phe	ctg Leu	ctt Leu 45	tat Tyr	ctg Leu	ggt Gly	cca Pro	cat His 50	ata Ile	gcc Ala	tca Ser	gtt Val	507
aca Thr 55	tta Leu	gct Ala	gct Ala	tat Tyr	gaa Glu 60	tgc Cys	aat Asn	tca Ser	gtt Val	aat Asn 65	ttt Phe	ccc Pro	gaa Glu	cca Pro	ccc Pro 70	555
tat Tyr	cct Pro	gat Asp	cag Gln	att Ile 75	att Ile	tgt Cys	cca Pro	gat Asp	gaa Glu 80	gag Glu	ggc Gly	act Thr	gaa Glu	gga Gly 85	acc Thr	603
att Ile	tct Ser	ttg Leu	tgg Trp 90	agt Ser	atc Ile	atc Ile	tca Ser	aaa Lys 95	gtt Val	agg Arg	att Ile	gaa Glu	gcc Ala 100	tgc Cys	atg Met	651
tgg Trp	ggt Gly	atc Ile 105	ggt Gly	aca Thr	gca Ala	atc Ile	gga Gly 110	gag Glu	ctg Leu	cct Pro	cca Pro	tat Tyr 115	ttc Phe	atg Met	gcc Ala	699
											gat Asp 130					747
Glu 135	Phe	Glu	Glu	Met	Leu 140	Glu	His	Ala	Glu	Ser 145	gca Ala	Gln	Val	Arg	Thr 150	795
gtg Val	ggg Gly	ata Ile	gaa Glu	aat Asn 155	aga Arg	aca Thr	ctt Leu	tac Tyr	ttc Phe 160	ttc Phe	cta Leu	aag Lys	agg Arg	cta Leu 165	tta Leu	843
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<210> 338
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<sup>&</sup>lt;211> 1347

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 138..671

<sup>&</sup>lt;221> sig\_peptide <222> 138..248

<sup>&</sup>lt;223> Von Heijne matrix score 3.5 seq LVFNFLLILTILT/IW

<sup>&</sup>lt;221> polyA\_signal <222> 1319..1324

<sup>&</sup>lt;221> polyA\_site

<222> 1338..1347

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aaga	acgo	יבני פ	gcgaa	gcas	ge de	icla:	ayı	y gc	19191		020		tta :	totas	ggcagt	120
caga	actgi	Ct t	aggo	caaat	בכ בו	gata	aaaa	age	CCCC	alc	cage	3666	tta taa	~~~	aggaat	170
ccca	agaa	iga d	rggg	gga a	atg 9	gag a	aga o	cag i	ca a	199	3CC 6	acg	cca y	gaa a	aag	1,0
				ľ	det (		_	in s	ser A	urg v			ser '	Glu 1	пÀр	
							-35					-30				210
gat	gag	tat	cag	ttt	caa	cat	cag	gga	gcg	gtg	gag	ctg	CLL	gtc	TTC	218
Asp	Glu	Tyr	Gln	Phe	Gln	His	Gln	Gly	Ala	Val	Glu	Leu	Leu	Val	Pne	
	-25					-20					-15					
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Asn	Phe	Leu	Leu	Ile	Leu	Thr	Ile	Leu	Thr	Ile	Trp	Leu	Phe	Lys	Asn	
-10					-5					1				5		
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His	Arg	Phe	Arg	Phe	Leu	His	Glu	Thr	Gly	Gly	Ala	Met	Val	Tyr	Gly	
			10					15					20			
ctt	aya	atg	gga	cta	att	tta	csa	tat	gct	aca	gca	cca	act	gat	att	362
Leu	Xaa	Met	Glv	Leu	Ile	Leu	Xaa	Tyr	Ala	Thr	Ala	Pro	Thr	Asp	Ile	
	••••	25	2				30	•				35				
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act		cta	att	aat	atc		gac	caa	att	tat		tat	aaa	tac	aar	458
Thr	Tou	Lou	Wal	λεν	Tle	Thr	Jan	Gln	Val	Tyr	Glu	Tyr	Lvs	Tyr	Lvs	
55	пеп	шец	vai	Woll	60	1111	vob	0111	Val	65	OI u	- 1 -	_,_	-1-	70	
						200	250	+	cat		~ ~ m	aa.	aat	gct		506
aga	gaa	ata	agt	cag	Cac	anic	Tla	2	Dwo	Tiin	Van	23.	Aan	712	Tla	300
Arg	GIU	тте	ser		HIS	хаа	TTE	ASI		urs	Add	GIÀ	MSII	Ala 85	116	
				75					80							EEA
ctt	gaa	aag	atg	aca	ttt	gat	cca -	raa	atc	TTC	TTC	aat	gtt	tta	tou	554
Leu	Glu	Lys		Thr	Phe	Asp	Pro		IIe	Phe	Pne	Asn		Leu	ьеu	
			90					95					100			600
cca	cca	att	ata	ttt	cat	gca	gga	tat	agt	cta	aag	aag	aga	cac	בכב	602
Pro	Pro	Ile	Ile	Phe	His	Ala	Gly	Tyr	Ser	Leu	Lys		Arg	His	Phe	
		105					110					115				
ttt	caa	aac	tta	gga	tct	att	tta	acg	tat	gcc	ttc	ttg	gga	act	gcc	650
Phe	Gln	Asn	Leu	Gly	Ser	Ile	Leu	Thr	Tyr	Ala	Phe	Leu	Gly	Thr	Ala	
	120					125					130					
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Ile	Ser	Cys	Ile	Val	Ile	Gly										
135					140											
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aaci	ttck	am :	aaata	acaa	aa c	ttca	aatc	a aa	qcaa	acta	waq	gatt	qct	ggac	tttctc	881
tate	gagti	tet (	ggact	ttct	ga c	ttag	ggaa	t at	ggat	cact	tac	ctta	aqt	tatg	tgaagc	941
gcat	ttac	att (	cttci	tttt	ac t	ttga	staa	t sc	cgat	atac	tca	ctac	att	cttt	tttgtc	1001
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															actctg	1241
~~	LLUd!		catt.		cy a	2222	gula tata	~ ty	ccas	etaa	tas	2000	3-t 22t	CCAG	cctcta	1301
													ual	ccay	cctctg	1347
ata	atcc	egt	ccaa	Laca	it a	aagc	LCCA	e eg	cagg	aaād	aad	aad				134/

<sup>&</sup>lt;210> 339 <211> 987

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<222> 124..411 <221> sig\_peptide <222> 124..186 <223> Von Heijne matrix score 6.30000019073486 seg MVALCCCLWKISG/CE <221> polyA signal <222> 948..953 <221> polyA site <222> 971..983 <400> 339 aagacgctgc ctttagggag agataaaaag cataatgaca ttagctagga aagttaattt 60 120 tcagttctta ctgaagtgct gtatgaaact gaaatttcca aggaactgaa ttttgtgagc caa atg agc atg caa ttc ttg ttt aag atg gtg gcc tta tgc tgt tgt 168 Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys -15 -10 ctc tgg aag atc tcc ggc tgt gag gaa gtc cct cta act tac aac ctg 216 Leu Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu - 5 264 ctc aag tgc ctc cta gat aaa gcg cac tgt gta ctc ctg aca cct tgt Leu Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys 20 ggt tac atc ttt tcc ttg atc agt cca gaa att ctc aaa ctc act tta 312 Gly Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu 35 360 atc act ttg cav atc ctc tta ata ctc aaa aat cta cac tta ctg tgg Ile Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp 50 55 408 ctg aca gtt tca agc awa tgt gtt cat cgc agt agt gca aga aaa gaa Leu Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu 65 aag tagaagaacc ctgcagagat ttgatggaac ccagcttcta ttcattaaaa 461 Lys 75 ccaatggcaa aatataaagc aaataggagg tgacgaaggt tacaaaaata cgtattgttt 521 581 atgttttccc tggggtgtgc tgattgtcag gcatcagttc cctgtgccat tcattcccca 641 acacagcatg catcagaaat tttatcaata aatgctttct ctctcaatgt tcaacctatg 701 ctgatagacc attaaataca gtttttgggt tcacagcttg tcatcatcat ttgtctatac ctgtggcaaa gaatatctaa taagatactc tcagcatttt gcacacttaa actaagatgc 761 821 tgaatgctgt attttacgga ataatcagcc acattaaatt tggagactca acaagcatgc 881 tgtgaacatt caacattagg tttaaatttt atttttaaaa gttaataata aaaggatata tgttaagtat tatgaaaccc tgcatatact gtaataaaat ggtggatgtg aatggacaat 941 atatgcaata aaatttataa tttgattcya aaaaaaaaaa aamccv 987

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<211> 748
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 372..494
<221> sig_peptide
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<223> Von Heijne matrix

<210> 340

score 5.30000019073486

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<221> polyA\_site <222> 1095..1106

<400> 341

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		<i>)</i> , <b>512</b>	50						-2	37-					10	. 1/11/20/02	•
Phe	Leu	Leu	Leu	Glu -5	Gly	Gly	Xaa	Thr	Glu 1	Gln	Val	Xaa	His 5	Ser	Glu		
														aga Arg		261	
		tac					999					gtg		tgc Cys		309	
	tca					gtg					gtc			cca Pro		357	
gtt					cct					cat				cct Pro 70	cgc	405	
tgc Cys	cca Pro	Glu	gac Asp	tcc	tta Leu	ccc Pro	cca Pro	gtg Val 80	aac	aat Asn	rwg Xaa	gtg Val	acc Thr 85	agc Ser		450	
ctct tatt tcctt atct cctc ggas aaac tggc acca aaaa	tttca tgtgg tgctg tccc ccacc gctct acaa taga ataga	gck and gcc and gcc and gcc and gcc and gcc and and gcc and gc	agtac atego ccaac gggtv accto gccga tggat accto agtgt	gcaac gacti wtgca cgcca acag ctccc acaa ccgg	cc cm cg cc ca gc cca gc cca gc cca gc cca gc cca gc cca at cca cca at cca cca at cca cca cca cca cca cca cca cca cca c	matca ccaa cgaga agaga ggaga caaga catgt cttga atcca	aatgo aatta atgga aagca gtoto catca tttoo gcatt	c caa c acc a acc a aga t co a gga c aat c gto	ccagt ctgto actgt acatt ccgct acca aggagt ggagt	gca gcct cctt ctt attg aga gtg	gctg tccc ggga acca ctgg tgca ccta tgct	gtteg cagto accgo gggco aaatt attet catgo	ggt gga etc etc etc eag egt eca eca	rggaa tgtto tgato tcact aagto catca tggco ttgta	grrggg aacktg ccarat ggtgat caccgg aataac gagtcc aatgtc cctcaa	570 630 690 750 810 870 930	
	2> DN 3> Ho		sapie	ens													
	)> l> CI ?> 11	_	366														
<222	sc	n He core	170 eijne 10.6	le mai 5999! LATG	99809		1										
	l> po 2> 11																
<22	l> po	olyA_	_site	2													

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Pro	Arg	Tyr 50	Ile	Xaa	His	Leū	Gly 55	Gln	His	Asn	Leu	Gln 60	Lys	gag Glu	Glu	359
Gly	Cys 65	Glu	Gln	Thr	Arg	Thr 70	Ala	Thr	Glu	Ser	Phe 75	Pro	His	ccc Pro	Gly	407
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Val	Xaa	Met	Xaa	Ser 100	Pro	Val	Ser	Ile	Thr 105	Trp	Ala	Val	Arg	ccc Pro 110	Leu	503
Thr	Leu	Ser	Ser 115	Arg	Cys	Val	Thr	Ala 120	Gly	Thr	Ser	Cys	Leu 125	att Ile	Ser	551
														acc Thr		599
_	_	_								_	_	_		aac Asn		647
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														gtc Val 190		743
														tgt Cys		791
														gtg Val		839
				acg Thr					taga	actg	gac (	ccac	ccac	ca		886
caq	cccat	tca d	ccct	ccatt	t c	cacti	taato	a ttt	tggti	tcct	qtto	cact	ctg 1	ttaat	caagaa	946
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<211> 1070

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 13..465

<221> sig\_peptide

<222> 13..75

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seq PVAVTAAVAPVLS/IN

<221> polyA\_signal <222> 1035..1040

<221> polyA\_site <222> 1060..1070

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cgg gaa att aaa aag caa ctg ctg ctt att gcg ggc ctt acc cgg gag Arg Glu Ile Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu 10 15 20	147
cgg ggc cta cta cac agt agc aaa tgg tcg gcg gag ttg gct ttc tct Arg Gly Leu Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser 25 30 35 40	195
ctc cct gca ttg cct ctg gcc gag ctg caa ccg cct ccg cct att aca Leu Pro Ala Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr 45 50 55	243
gag gaa gat gcc cag gat atg gat gcc tat acc ctg gcc aag gcc tac Glu Glu Asp Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr 60 65 70	291
ttt gac gtt aaa gag tat gat cgg gca gca cat ttc ctg cat ggc tgc Phe Asp Val Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys 75 80 85	339
aat gca aga aaa gcc tat ttt ctg tat atg tat tcc aga tat ctg gtg Asn Ala Arg Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val 90 95 100	387
agg gcc att tta aaa tgt cat tct gcc ttt agt gaa aca tcc ata ttt Arg Ala Ile Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe 105 110 115	435
aga acc aat gga aaa gtt aaa tct ttt aaa tagcttagca gtgggccact Arg Thr Asn Gly Lys Val Lys Ser Phe Lys 125 130	485
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<210> 344

<211> 1213

<212> DNA

<213> Homo sapiens

<220>

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55

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gca agg gtt cgt aac cga tgc tct aaa gac tgg cct tgt aat tat gac Ala Arg Val Arg Asn Arg Cys Ser Lys Asp Trp Pro Cys Asn Tyr Asp 80 85 90	640
tgg gat tcg gac gat gat gca gag gtt gag gct atc ctc aat tca ggt	688
Trp Asp Ser Asp Asp Asp Ala Glu Val Glu Ala Ile Leu Asn Ser Gly 95 100 105	
gct arg ggt tat tcc gcc cct taagtaratc tgaggcagac ccttgggggt	739
Ala Xaa Gly Tyr Ser Ala Pro	
110 115	
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Val Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly	
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Leu Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val	
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Val Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe	231
10 15 20	
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Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys	
25 30 35 40	
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Ala Arg Leu Leu Thr His Trp	
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530

590

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  atg aga act tta ttt ggt gca gtc agg gct cca ttt agt tcc ctc act
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          -25
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  Leu Ser Leu Arg Ser Ala Met Ser
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aaa aaa atc ttt tta ttt tat gcc ttc awa ggt tgc ycg ttt car agt Lys Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser 35 40 45	374
gcc aca taaataaaat gtttaacaaa aaaaaaaaaa	409
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cct cts sta gct gag ccc act gca gag ggg gag cca cac ctg ccc acg Pro Leu Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr	158

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gct gtc ttg cca acc Ala Val Leu Pro Thr 25	atg act gct tt	t geg age gge etg g	
gga sca vma tgt gtt Gly Xaa Xaa Cys Val	tgt tca aat tt	t act gaa gga ccc o	
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gga tgg gca cta tga Gly Trp Ala Leu	cscccgg gccagag		
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atg aag acg tct gac Met Lys Thr Ser Asp -55	act att atc co		
gcc att ggc acc tgc Ala Ile Gly Thr Cys -35	ttc ggc tac to		
tac ttc ctt gcc tac	ctg tgc aac go	cc cag atc acc atg	ctg cag atg 242

•			Ala -20	-				-15					-10				
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		-5	Leu		_		1				5						
			aat													33	8
	Thr	Tyr	Asn	Ile		Leu	Arg	Ala	Leu		Tyr	Leu	Phe	Trp			
10					15					20				~+~	25	38	۷
			gga													36	О
ьeu	vai	GIY	Gly	ьеu 30	Ser	TILL	Leu	AIG	35	vaı	Ala	vai	Deu	40	Jei		
caa	acc	ata	ggc		aca	cad	caa	mta		ctc	tat	aac	acc		gct	43	4
			Gly														
_			45					50					55				
			atg													48	2
Ala	Leu		Met	Leu	Phe	Leu		Tyr	Leu	His	Phe		Tyr	His	Lys		
٠.		60	•				65					70				53	^
			ggg Gly													33	٠
лаа	75	Add	GIĀ	116	теп	80 80	TIII	Бец	GIU	GIY	85	ASII	110	FIO	110		
atc		agg	gtc	ccc	aga		atc	cct	acc	atq		cct	qct	gct	cgg	57	8
			Val														
90		_			95	-				100					105		
			acc													62	6
Leu	Pro	Thr	Thr		Leu	Asn	Ala	Thr		Lys	Ala	Val	Ala		Thr		
				110					115					120		67	0
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neu	GIII	Ser	125														
act	gcag	aga (		gaas	ac ta	attaa	aaqq	a ca	atcci	tgat	gaca	atqti	ttc (	gtaga	atgggg	73	8
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															tgcaga		8
aaa	tggg	tca :	gctc	cttt	ga ga	aacc	cctc	c cc	accta	accc	ctt	cctt	cct	cttta	atctct	91	
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Met Gly Trp Gln Arg	
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Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser Ala His Pro Pro Gln	244
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Met Met Ser Ser Glu Leu Arg Arg Asn	434
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Pro His Phe Leu Lys Ser Asn Leu Phe Leu Gln Leu Leu Val Ser His	
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Glu Ile Val Cys Ala Thr Glu Thr Val Thr Thr Asn Phe Leu Arg His	

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Leu		Leu	Ala	Ala	Ala		Gly	Ala	Val	Ala		Phe	Leu	He		
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AL Y	TIE	ττħ	val	10	μeu	n. y	261	1.15 C	15	νат	1111	-10	A	20	JU1	
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Phe	Leu	Ile	Tyr	Val	Leu	Thr		Thr	Ala	Ser	Ala	Ala	Thr	Val	Ala	
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Thr	Val	Phe	Leu		Gln	Tyr	Leu	Phe		Thr	Pne	Pro	Arg	116	vai	
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Phe	Met	Leu			Val	Val	Val		Xaa	Phe	Leu	Leu	GIA	GIY	Tyr	
			180					185					190			703
ctg	ttg	ttt	gtc	ctg	tat	ctg	gcg	gcc	acc	aac	cag	act	act	aac	gag	783
Leu	Leu	Phe	Val	Leu	Tyr	Leu		Ala	Thr	Asn	Gln	Thr	Thr	Asn	GIU	
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Trp	Tyr	Arg	Xaa	Asp	Trp		Trp	Cys	Gln	Arg	Cys	Pro	Leu	vai	Ala	
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Trp	Pro	Pro	Ser	Ala	Glu	Pro	Gln	Val	His		Asn	Ile	His	Ser	HIS	
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His	Glu	Arg	Lys	Lys	Gln	Glu										
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Met Thr Gly Phe Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg

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Pro Ser Ser Phe Val Ala Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys -25 -20 -15	
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Val Pro Gly Ala Ser Pro Thr Thr Leu Ala Phe Pro Pro Val Xaa Leu -10 -5 1 5	
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Thr Gly Pro Xaa Thr Asp Gly Ile Pro Phe Ala Leu Xaa Ser Ala Ala 10 15 20	
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Gly Pro Phe Cys Ala Ser Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly 25 30 35	
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Pro Leu Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser 40 45 50	
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araaratgtt catcggaact aaraatgakt ttaacaggtc agttttttga gtgaatgtg	g 540
gaaaraacac agcatacaga atggctaacc atgaaagttc atgaaagcgt kgaaaaaat	c 600
aaatcaaatc ataattagat atgaagt atg cta rag ctt tca agg gct aca aa Met Leu Xaa Leu Ser Arg Ala Thr Ly	aa 654 ⁄s
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Xaa Gly Arg Ala Arg Trp Leu Met Pro Val Ile Pro Ala Leu Gln Glu -15 -10 -5	
gcc gan gca ggc gga tca cga ggt cag gag ttt gaa act agc ctg gcc	750

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ttg c Leu G		gaa	ctga	ga t			t go	acto	cago	ttg		aaca	gag	caaga	act	854
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gca d	cac	tct	tta	tca	ctg	aga	gac	gtc	tca	gag	agg	ctg	tgc	agc	tgc	207
Ala H		Ser 20	Leu	Ser	Leu	Arg	Asp 25	Val	Ser	GIu	Arg	ьеи 30	Cys	ser	Cys	
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Trp A	Arg 35	Thr	Ile	Ser	Met	Gly 40	Pro	Cys	Ala	Arg	45	Sei	PIO	Mec	ASII	
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Leu			Gln			-			_							
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Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys
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Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn
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Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr
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                                                                     1186
aaccccagca gtcctgggcc ccctgggaga gtgctcaacc tacagtggag ggagactgac
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Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala Val Thr
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Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys Arg Phe
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<sup>&</sup>lt;222> 19..567

<sup>&</sup>lt;221> sig\_peptide

<sup>&</sup>lt;222> 19..63

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cat	cga	rat	att	aaa	999	caa	aat	gtc	ttg	ctg	act	gaa	aat	gca	gaa	396
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gac	ttg	rgg	CCC	ttg	ggt	atc	acc mb~	310	דום	gaa	Mot	yca Nin	Glu	ggg Gly	LAU	300
Asp	ьeu	11p	ser	Leu	GIÀ	TIE	110	Ald	116	GIU	Mec	115	Giu	GLY	Deu	
								+	~~~~		a++ a			ceca	raato	642
								Lya	gage			Juca		cccg	gaatc	012
PIO	120	261	Val	TIII	Cys	125	PIU									
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cag	tact	222		aayi	rc d	ayadı	9-99	r ce	aaad.	2202	att.	rato	aar i	cato	agagct cattta	762
you.	rage	aad i	addi(	acd;	90 C	ayog	accd!	2 GG	a-ay	acet	Case	7020	-45 '	atto	atagaa	822
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<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

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<sup>&</sup>lt;222> 39..458

<sup>&</sup>lt;221> sig\_peptide

<sup>&</sup>lt;222> 39..80

<sup>&</sup>lt;223> Von Heijne matrix
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<sup>&</sup>lt;221> polyA\_signal

<sup>&</sup>lt;222> 613..618

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-10

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agg aac tgg ctg cca acc cct ccg gct acg ggc ccc tta ccg agc tcc Arg Asn Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser 20 25 30	146
cag act ggt cat atg cgg atg gcc gcc ctg ctc ccc caa tgaaaggcca Gln Thr Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 35 40	195
gettegaaaa aaagetgaaa gggagacktt tgeaaracra kttgtactge tgteacagga aatggaeget ggattacaas catggeaset caggeagear aakttgeagg aaraacaaag gaageaggaa aatgetetta aacecaaagg ggetteaetg aaaaseccae tteeaaktea ataaaaagea acteetgeet eeetteetea eeetteete ggatteett teetateaeet aratgettea teeageeara aaatageett eaekkteeee atetgette arageaaaar agetgggaem eeaaraacaa getgttarat eaetgeetgg gaggettgge ttartaetet eatetetggt teeatteeag teeagetaag tettgettta aaatttttae eteetagetg ggtgeggtgg eteaegeetg taateceage actttgggag getgaggegg geagateaea agateaggag ttegagaeea geetggeeaa eeeageetgg teaacatggt gaaaeeetgt eeetactaaa gatacaaaca attageeggg egtggtgggg tgegettgta ateeeageta eteaggagge tgaggeagga gaategetta aactegggag gtagaggttg cagtgageea aggteacace attgeactee aacetgggeg acagggegag actetgtete aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa	255 315 375 435 555 615 675 735 795 855 915 918
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tcc ttg ctg cgg tcg gag aag tgg aac cac aca ctt tcc atg gct ctc Ser Leu Leu Arg Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu 10 15 20	193
atc ctc ttc tgc aac tac tat gtt tta ttt aaa ctt ctc cgg gac aga  Ile Leu Phe Cys Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg  30 35 40	241

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			act Thr 235													975
			gaa Glu													1023
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<222> 1027..1040

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Me	et Glu Glu										
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30 35	40										
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Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu											
45 50											
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-40

-35

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Glu Cys Ile Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val

	-30					-25					-20					
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Ala	Gly	Ile	Leu	Phe		Thr	Gly	Trp	Trp		Met	Ile	Asp	Ala		
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Val	Val	Tyr		Lys	Pro	GIu	Gin	Leu 10	Asn	His	Ala	Pne	H15	Thr	Cys	
aat	at a	+++	5	202	tta	act	ttc		ata	at a	aat	act		tcc	aat	302
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GLY	• • • •	20	501				25					30				
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	35					40					45					
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_	Ala	Arg	Val	Trp		Phe	Ile	Gly	Phe		Leu	Met	Phe	Gly		
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														Leu		
	•		85		_			90					95			
														cta		542
Phe	Phe		Thr	Leu	Ile	Tyr		Phe	Gly	Arg	Thr		Glu	Leu	Trp	
		100					105					110				
	tga	gatca	act 1	cctta	aagto	ca ca	attt	ccti	tt	gttat	tatt	ctgi	tttg	tag		595
Thr	~~++			- a + a	aa t		stta		ato	72 <b>0</b> t	2021	tat:	1	rtaas	atgttt	655
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	_	•	•	-		_			_		_	-			catcat	835
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															tgagac	955
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ctg gaa agg gtg aaa aga aga tgc cta gag aat ggc aat tta aaa gaa Leu Glu Arg Val Lys Arg Arg Cys Leu Glu Asn Gly Asn Leu Lys Glu 60 65 70	341
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<222> 155..340

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 score 3.70000004768372
 seq SILGIISVPLSIG/YC

<221> polyA\_signal

<222> 912..917

<221> polyA\_site <222> 937..947

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ccttgacctg accgacactg gttcccatga agcggctacc	<b>3</b> 3
tggtagaatc gacattctgg tcaacaatgg tgga atg to	
	er Gln Arg Ser Leu Cys
	-60
atg gat acc agc ttg gat gtc tac aga rag cta	ata gag ctt aac tac 223
Met Asp Thr Ser Leu Asp Val Tyr Arg Xaa Leu	Ile Glu Leu Asn Tyr
-55 -50 -45	-40
tta ggg acg gtg tcc ttg aca aaa tgt gtt ctg	
Leu Gly Thr Val Ser Leu Thr Lys Cys Val Leu	
-35 -30	-25
agg aag caa gga aag att gtt act gtg aat agc	
Arg Lys Gln Gly Lys Ile Val Thr Val Asn Ser -20 -15	-
	-10
tct gta cct ctt tcc att gga tac tgt gct agc Ser Val Pro Leu Ser Ile Gly Tyr Cys Ala Ser	
-5 1	bys his Aid Ded Aig
ggt ttt ttt aat ggc ctt cga aca gaa ctt qcc	aca tac cca qqt ata 415
Gly Phe Phe Asn Gly Leu Arg Thr Glu Leu Ala	
10 15 20	25
ata gtt tct aac att tgc cca gga cct gtg caa	tca aat att gtg gaa 463
Ile Val Ser Asn Ile Cys Pro Gly Pro Val Gln	
30 35	40
aat tcc cta gct gga gaa gtc aca aaa act ata	
Asn Ser Leu Ala Gly Glu Val Thr Lys Thr Ile	Gly Asn Asn Gly Asn
45 50	55
cag tee cae aag atg aca ace agt egt tgt gtg	
Gln Ser His Lys Met Thr Thr Ser Arg Cys Val	_
60 65	70
age atg gee aat gat ttg aaa gaa gtt tgg ate	<del>-</del>
Ser Met Ala Asn Asp Leu Lys Glu Val Trp Ile 75 80	85
ttg tta gta aca tat ttg tgg caa tac atg cca	
Leu Leu Val Thr Tyr Leu Trp Gln Tyr Met Pro	
90 95 100	105
ata acc aac aag atg ggg aag aaa agg att gag	
Ile Thr Asn Lys Met Gly Lys Lys Arg Ile Glu	·
110 115	120
gtg gat gcm rac tct tct tat ttt aaa atc ttt	aag aca aaa cat gac 751
Val Asp Ala Xaa Ser Ser Tyr Phe Lys Ile Phe	Lys Thr Lys His Asp
125 130	135
tgaaaaganc acctgtactt ttcaagccac tggagggaga	aatggaaaac atgaaaacag 811
caatcttctt atgcttctga ataatcaaag actaatttgt	_
atgactttgc ttccaacatg grrtgaaata aaaaataaat	
cttgcaaaaa aaaaaa	947

<sup>&</sup>lt;210> 377

<sup>&</sup>lt;211> 621 <212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 46..585

<sup>&</sup>lt;221> sig\_peptide

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<222> 46..120

<sup>&</sup>lt;210> 378

<sup>&</sup>lt;211> 52

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> SIGNAL

<sup>&</sup>lt;222> -20..-1

<sup>&</sup>lt;400> 378

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Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val Leu Gln Leu Thr Thr

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-20 -15 -10 -5
Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val Asn Pro Phe Glu Xaa
Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala His His Phe Ile His
             20
Pro Cys Leu Asp
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<210> 379
<211> 193
<212> PRT
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<221> SIGNAL
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<400> 379
Met Val Val Leu Arg Ala Gly Lys Lys Thr Phe Leu Pro Pro Leu Xaa
                       -15
Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro Glu Arg Gly Ala
                    1
                             5
Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg Phe Cys Pro Pro
                              20
         15
Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp Lys Tyr Ser Asn
            30
                          35
Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu Ser Pro Leu Glu
                       50
Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu Trp Asn Gln Gln
   60 65
Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu Lys Glu Glu Phe
75 80
Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu Arg Thr Glu Ser
             95
                              100
Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala Asp Phe Tyr Lys
                            115 120
           110
Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr Tyr Asn Arg Asp
                                         135
        125
                         130
Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met Gly Lys Val Ala
     140 145 150
Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln Lys Lys Arg Ser
Asn
170
<210> 380
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 380
Met Ala Phe Thr Leu Xaa Ser Leu Leu Gln Ala Ala Leu Leu Cys Val
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Asn Ala Ile Ala Val Leu His Glu Glu Arg Phe Leu Lys Asn Ile Gly 10 Trp Gly Thr Asp Gln Gly Ile Gly Gly Phe Gly Glu Glu Pro Gly Ile 25 Lys Ser Xaa Xaa Met Xaa Leu Ile Arg Ser Val Arg Thr Val Met Arg 45 40 Val Pro Leu Ile Ile Val Asn Ser Ile Ala Ile Val Leu Leu Leu 55 Phe Gly <210> 381 <211> 198 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 381 Met Pro Val Pro Ala Leu Cys Leu Leu Trp Ala Leu Ala Met Val Thr -20 -15 Arg Pro Ala Ser Ala Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His 1 Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala 20 15 Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Arg Leu Thr Lys Ala Arg Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu 50 Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu 65 70 Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr 85 Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100 95 Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro 120 115 110 Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn 130 His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu 145 150 Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His 165 Thr Ala Ala Leu Pro Ala 175 <210> 382 <211> 160 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -55..-1

Met Asp Lys Leu Lys Lys Val Leu Ser Gly Gln Asp Thr Glu Asp Arg

<400> 382

-50 -45 Ser Gly Leu Ser Glu Val Val Glu Ala Ser Ser Leu Ser Trp Ser Thr -35 -30 Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser -15 -20 Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr 20 15 Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro 35 30 Thr Arg Leu Ile Ala Thr Ile Met Val Leu Leu Cys Phe Ala Leu Thr 50 4.5 Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe 65 Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile 80 85 Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala 100 95

<210> 383 <211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 383 Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val -10 -5 -15 Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly 25 20 Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro 35 40 Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met 70 Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro 85

<210> 384 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

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Gln Lys Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val
                35
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<210> 385
<211> 27
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 385
Met Gly Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser
-15 -10 -5
Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn
<210> 386
<211> 186
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 386
Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile
                        -10
                  -15
Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser
               1 5
Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
                       20
      15
Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
 30 35
Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
                                 55
                 50
Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys
                               70
               65
Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
           80
                            85
Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu
                         100
Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly
                      115
     110
Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser
                   130
                                   135
Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile
               145 150
Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser
             160
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<210> 387
<211> 179
<212> PRT
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<222> -26..-1
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Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
                              15
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
                           30
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
                       45
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                   60
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                 80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                              95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                          110
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                    125
                                130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
                            145
                  140
Ile Xaa Leu
<210> 388
<211> 150
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 388
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
        -50
                                      -45
Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
                                   -30
               -35
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
                               -15 -10
Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
                 15
                                     20
Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
                                35
Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
                              50
Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala
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65

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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser
           80
Pro Gly Cys Tyr Arg Tyr
<210> 389
<211> 236
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys
                  -25
Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala
              -10
                               -5
Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Ser Leu Phe Asp Leu
                          10
Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu
                     25
Arg His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser
                   40 45
Met Ala Pro Ala Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala
                55 60
Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser
             70 75
Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu
                           90
Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser
    100 105
Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro
  115 120
                                      125
Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp
                135
                                   140
Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu
       150
                               155
Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro
                           170
Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly
                        185 190
Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg
                     200
<210> 390
<211> 149
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<221> SIGNAL
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Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
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WO 99/31236
Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Prc Ser Ala Met Thr
                     -75
             -80
Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
                              -55
         -65 -60
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
                                       -40
          -45
      -50
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
                  -30 -25
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
                     -10
              -15
Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile
                                     10
                    5
Pro Lys Leu Asn Arg Phe Leu Leu Phe Ile Gly Phe Val Cys Val
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Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro
                  35
Gly Tyr Leu Met Gly
<210> 391
<211> 69
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -49..-1
<400> 391
Met Pro Phe His Phe Pro Phe Leu Gly Phe Val Cys Leu His Leu His
                              -40
             -45
Leu Thr Pro Cys Leu Thr Val Pro Arg Arg Pro Leu Phe Leu Leu
                     -25
         -30
His Leu Cys Pro His Leu Pro Phe Leu Leu Leu Ser Cys Val Gly
     -15 -10 -5
Xaa Xaa Pro Ser Cys Leu Pro Ser Ser Ser Thr Cys Val Ser Leu His
Phe Phe Ile Pro Asp
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<210> 392 <211> 241 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1 <400> 392 Met Gly Thr Ala Ser Arg Ser Asn Ile Ala Arg His Leu Gln Thr Asn -25 -20 Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr Leu Ser Val -5 -10 Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu Ala Val Thr 10 Ile Lys Cys Thr Phe Ser Ala Thr Gly Cys Pro Ser Glu Gln Pro Thr

Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 55 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 110 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 120 125 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 140 135 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 150 155 160 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln 170 175 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 205 Pro

<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1 <400> 393 Met Asn Cys Asn Val Val Ser Glu Arg Gly Lys Trp Leu Glu Val Glu -25 -20 Cys Ser Leu Met Thr Cys Thr Thr Leu Ile Asn Ala Ser Ala Ile Ser -5 -10 Thr Asn Thr Leu Thr Asp Met Gly Ser Phe Asp Arg Arg Glu Ser 10

<210> 394 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 394 Met Ala Phe Gly Leu Gln Met Phe Ile Gln Arg Lys Phe Pro Tyr Pro -25 -20 Leu Gln Trp Ser Leu Leu Val Ala Val Val Ala Gly Ser Val Val Ser -10 - 5 Tyr Gly Val Thr Arg Val Glu Ser Glu Lys Cys Asn Asn Leu Trp Leu 10 15 Phe Leu Glu Thr Gly Gln Leu Pro Lys Asp Arg Ser Thr Asp Gln Xaa 25 30 35

Ser

<210> 395

<211> 73

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

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<400> 395

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro

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Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys
-5 1 5

Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 10 15 20

Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 25 30 35 40

Trp Gly Gln Gly Thr His Ser Ser Leu

45

<210> 396

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 396

Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr
-15 -10 -5

Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu
1 5 10

Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu 15 20 25 30

Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala 35

<210> 397

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -93..-1

<400> 397

Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn

-90 -85 -80
Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val

-65 -70 -75 Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr -50 -60 -55 Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val -40 -35 Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn -25 -20 Val Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu -10 -5 Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu 10 Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys 30 25 Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly 45 50 40 Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn **.**55 60 Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys 70 75 Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln 90

<210> 398

<211> 149

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -72..-1

<400> 398

Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe
-70 -65 -60

Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu
-55 -50 -45

Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys
-40 -35 -30 -25

Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -20 -15 -10

Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala
-5 5 5

Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 10 15 20

Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr
25 30 35 40

Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln
45 50 55

His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 60 65 70

Phe Ser Met Val Gly

75

<210> 399

<211> 73

<212> PRT

<213> Homo sapiens

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<220>
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Leu Ala Gln Ala Leu Asp Cys His Val Cys Ala Tyr Asn Gly Asp Asn
                                          10
             1
Cys Phe Asn Pro Met Arg Cys Pro Ala Met Val Ala Tyr Cys Met Thr
           20
                                       25
 15
Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met Lys Val Ser Lys Ser Cys
                  35
Val Pro Arg Cys Phe Glu Xaa Cys Val
<210> 400
<211> 86
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<222> -20..-1
<400> 400
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
-20 -15
                                 -10
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
            1
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
                        20
                                 25
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
                    35
                                      40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
                          55
               50
Pro Xaa Lys Leu Arg Gln
             65
<210> 401
<211> 78
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
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<400> 401
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                     -15
Pro Gly Leu Trp Gln His Leu Thr Ala Asn His Trp Pro Pro Phe Ser
                 1
Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser Glu Gln Ile Ser Glu
          15
                            20
                                             25
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Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg Ser Leu Asn Gln Glu

30 35 40 Pro Phe Val Ser Arq Ala Ile Arg Pro Lys Tyr Ser Ile Thr 45 50 55

<210> 402 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -28..-1

<210> 403 <211> 211 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1

<400> 403 Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr -20 Phe Phe Ser Gly Val Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn 30 Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His 45 Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro 60 Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser 75 80 Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser 95 Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu 105 110 Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys 125 Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln 140 145 Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe 160 155 Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr 175 170

Arg Ser Ile

<210> 404 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -80..-1 <400> 404

Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp -70 -75 Ser Val Arg Ile Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr -55 -60 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -40 -45 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -25 ~30 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro -10 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 10 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 25

40

Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu

<210> 405 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1

 Met Glu Lys
 Ser Trp
 Met Leu Trp
 Asn Phe Val Glu Arg
 Trp Leu Ile

 -25
 -20
 -15
 -15

 Ala Leu Ala Ser Trp
 Ser Trp Ala Leu Cys
 Arg Ile Ser Leu Leu Leu Pro

 -10
 -5
 1
 5

 Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu Leu 10
 15
 20

 Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys
 Phe Xaa Asp Val Leu 25

 Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His 40
 45
 50

 Ala His Trp Xaa Ser Xaa 60
 60

<210> 406 <211> 162 <212> PRT <213> Homo sapiens

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 <222> -31..-1
 <400> 406
 Met Ala Ala Arp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
                               -20
                       -25
 Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
                              -5
                   -10
 Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
                           10
  Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn
                                     30
                           25
  Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val
                                 45
                     40
 Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn
                                     60
      55
 Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser
                                 75
                70
. Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser
                           90
 Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys
                         105
                                   110
  Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu
                      120
 Pro Asn
 130
 <210> 407
  <211> 98
 <212> PRT
 <213> Homo sapiens
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<220>
<221> SIGNAL
<222> -37..-1
<400> 407

Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile -30 -35 Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe -15 -10 Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu 1 Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln 20 Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu. Tyr Leu Leu Gly 35 Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met 50 Val Arg 60

<210> 408 <211> 70 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
-15 -10
                      -5 1
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
   5 10
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
          25
20
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
 35 40
Asp Phe Ser Ser Phe Thr
50
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
             -40 -35
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
           -25 -20 -15
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
   -10 -5 1
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
  5 10
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 410
Met Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser
     -20 -15 -10
Ser Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys
             1
Asn Pro Phe Leu Trp Lys Leu
            15
<210> 411
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<211> 51 <212> PRT

<213> Homo sapiens <220> <221> SIGNAL <222> -23..-1 <400> 411 Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala -10 -15 Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly 1 Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg 20 15 10 Ile Trp Pro <210> 412 <211> 95 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -48..-1 <400> 412 Met Ala Ser Ser His Trp Asn Glu Thr Thr Ser Val Tyr Gln Tyr -40 -35 Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn -25 -20 Thr Ala Cys Phe Val Ile Leu Leu Leu Phe Ile Phe Thr Val Val Ser -10 -5 Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys 1 5 10 Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu 25 20 Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val <210> 413 <211> 60 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1 <400> 413 Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly -30 -25 -20 Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys -5 -10 Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser

10

25

5

20

Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser

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<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
<400> 414
Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro
             -75
                    -70
Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly
          -60 -55
Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe
   -45 \ -40
                               -35
Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln
  -30 -25
                           -20
Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe
-15
              -10
                               -5
Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa
   5
              10
Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Ala Gln Pro Thr Phe
                    25
Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa
                  40
Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala
                55
                                 60
Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln
            70
His Tyr Ile Arg His Ala Arg Gly Gly Leu
<210> 415
<211> 190
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<211> 190
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -82..-1
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<400> 415 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 -55 Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 -25 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -15 -10 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile 20 25 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu

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<210> 416
<211> 114
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 416
Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg
                   -55
                                       -50
Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly
               -40
                                   -35
Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu
           -25
                               -20
                                                  -15
Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val
                          -5
Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys
                  10
                                      15
Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys
              25
                                   30
Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser
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<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -108..-1 <400> 417 Met Thr Ser Gly Gln Ala

Ser Lys

Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln Ser Pro Gln Ala Leu -100 -105 Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser Ile Thr Leu Thr Leu -85 -80 Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg Asn Val Thr His Leu -70 -65 Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu Ser Gly Arg Glu Ala -55 -50 His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro Thr Ala Trp Ser Ser -40 -35 Asp Asp Cys Ala Leu His Gly His Cys Glu Gln Val Val Phe Thr Ala -25 -20 Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe Pro Ser Leu Tyr Ser WO 99/31236 -311- PCT/IB98/02122

<210> 418 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 418 Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu -15 -10 Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val 1 5 Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val 20 Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro 30 35 Leu Arg Met 45

<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 419

Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp -25 Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln -10 Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser 40 Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe **5**5 Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 70 Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 85 90 Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser 105

Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 120 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 140 135 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 150 155 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 165 170 175 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 185 190 180 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 205 195 200 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 220 215 Leu Phe Phe Tyr Asp Gln His Gly Glu Val Ile Gly Val Leu Trp 230 235 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 250 255 245 Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 275 280 285 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 295

<210> 420 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 420 Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser Phe His -10 -15 Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser Arg His 5 10 His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu Glu Asn 20 25 Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys Ile Val 35 3.0 40 Gly

<210> 421 <211> 57 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

Met Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser -30 -25 -20 -15
Thr Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val

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-5
              -10
Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala
   5 10
Glu Glu Gln Lys Xaa Ser Gly Ile Met
<210> 422
<211> 85
<212> PRT
<213> Homo sapiens
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<222> -17..-1
<400> 422
Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
 -15 -10
Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser
               5
                                    10
 1
Asp Ser Asp Glu Leu Ala Ser Gly Kaa Phe Val Phe Pro Tyr Pro Tyr
                              25
             20
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
                            40
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
                        55
Leu Pro Ser Glu Lys
  65
<210> 423
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 423
Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val
     -15
Gly Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser
                                     10
Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr
                                25
Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe
                          40
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
                    55
Leu Pro Ser Glu Lys
  65
<210> 424
<211> 69
<212> PRT
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<213> Homo sapiens

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<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
                   -20 -15
          -25
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
               -5 1
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
           10 15
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                       30
20 25
Gln Xaa Ala Leu Leu
        40
<210> 425
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
                       -45
-55 -50
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
            -35 -30 -25
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
                         -15 -10
            -20
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
        -5 1 5
Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu
      15
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
25 30 35
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
          45
Val Pro Ser Trp Val Gln Phe Phe Leu Gly
        60
<210> 426
<211> 41
<212> PRT
<213> Homo sapiens
<221> SIGNAL
<222> -30..-1
<400> 426
Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly
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Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln

- 5

-25

-10

-20 -15

Arg Cys Ser Gly Ser Pro Leu Pro Leu

<210> 427 <211> 50 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1 <400> 427

Met Ala Pro His Thr Ala Ser Phe Gly Val Cys Pro Leu Leu Ser Val -35 . -30 -25 Thr Arg Val Val Ala Thr Glu His Trp Leu Phe Leu Ala Ser Leu Ser -15 -10 -5 Gly Ile Lys Thr Tyr Gln Ser Tyr Ile Ser Val Phe Cys Lys Val Thr

1 5 10

Leu Ile

<210> 428 <211> 136 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 428 Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala -10 -5 -15 Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu 5 10 Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg 20 25 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Leu Ala Thr Leu 35 40 Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 55 50 Met Val Gly Gly Glu Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly 70 75 Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg 90 85 Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 105 95 100 Met Pro Gly Leu Ser Gly Val Leu

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

115

<220>

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<221> SIGNAL <222> -65..-1 <400> 429 Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 -55 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 -40 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -25 -30 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -15 -10 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 20 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp 55 Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 75 Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 90 85 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 100 105 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120 Val Ser <210> 430 <211> 141 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -69..-1 <400> 430 Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -60 -65 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -45 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -35 -30 -25 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser 1 5 Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa

Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa 30 35 40
Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln

45 50 55 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly

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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 431
Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
              -65
                                -60
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
                -45
         -50
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
     -35 -30
                                 -25
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                 -15
                             -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
                 1
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Phe Ile
                            20
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
    30
                         35
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
                    50
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                 65
                                   70 -
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
             80
                                85
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
                            100
         95
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
      110
                        115
                                 120
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
                    130
                                      135
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
           145 150
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
             160
Gly Tyr Glu Glu Leu Leu Thr Ser
<210> 432
<211> 49
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Phe

<210> 433

<211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 433 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 -5 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 . Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 55 His Arg Ile Cys Asp Leu 70

<210> 434 <211> 144 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 434

Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -20 -15 · Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala 30 Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu 60 65 Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser 80

<210> 435 <211> 121

<213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 435 Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala -10 Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln 10 Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser 20 25 Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser 40 Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg 70 . Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala 85 90 Leu Gly Ser Gly Glu His Pro Xaa Xaa 100

<210> 436 <211> 162 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 436

<212> PRT

Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala -10 Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln 5 10 Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser 25 Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys 40 Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro 60 55 Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly 70 75 Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu 85 90 Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Leu Gln 105 Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu 120 125 Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln 130 135 Glu Gly 145

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<210> 437
 <211> 110
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -20..-1
 <400> 437
 Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
 -20 -15
                               -10
 Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
                                        10
 Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
                          20
 Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
                            40
                      35
 Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
                   50
                           55
. Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
 Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
           80
                              85
 <210> 438
 <211> 71
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -15..-1
 Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
                 -10
                                    -5
 Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                               10
 Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
                          25
 Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
 Gln Val Pro Arg Arg Ala Gly
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 <210> 439
 <211> 99
 <212> PRT
 <213> Homo sapiens
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 <222> -24..-1
 <400> 439
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Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys

-15

-20

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      Ser Leu Asn Thr
      Leu Leu Leu Leu Gly Gly Val Asn Lys Ile Ala Glu Lys

      -5
      -5
      -5
      1
      5
      1
      5

      Ile Cys Gly Asp Leu Lys Asp Pro Cys Lys Leu Asp Met Asn Phe Gly 10
      15
      20
      20
      8
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<210> 440
<211> 169
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -25..-1

<400> 440

Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu -20 -15 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala 15 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu 50 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr 65 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser 80 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val 110 115 Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp

130

125

Arg Thr Pro Asp Leu Pro Ala Leu Ala 140

Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 -50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -40 -35 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -25 -20 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro -10 -5 Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 15 20 10 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 30 25 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser 75 Tyr Ser Thr Lys Arg Ser Pro

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 442 Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg -10 Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg 10 Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Xaa Arg Thr Lys Tyr Glu 25 30 Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly Gly Asn Xaa Xaa Xaa

Xaa Leu Ser Lys Arg Asp

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1 <400> 443 Met Ser Trp Thr Val Pro Val Val Arg Ala Ser Gln Arg Val Ser Ser -30

Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu Cys Pro Arg Gln -10 Ala Thr Arg Ile Pro Leu Asn Gly Thr Trp Leu Phe Thr Pro Val Ser

-25

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Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
                                  25
               20
Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
           35
                             40
Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
                          55
Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
                       70
Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
                                  105
Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
           115
                              120
Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
                          135
Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
                      150
                                         155
Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
                  165
                                     170
Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
              180
                                 185
Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
           195
                             200
Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
                          215
Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
           230
                                         235
Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                  245
                                     250
Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
              260
                                 265
Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
                             280
           275
Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                                            300
                          295
Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
                      310
                                        315
Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
               325
                                     330
Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
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<210> 445 <211> 50

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                                            -25
               -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                  -15
 -20
                              -10
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                              5
-5
               1
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
               -20
                                        -15
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
                -5
                                    1
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
       10
Thr Arg Gly
      25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
                  -25
                                     -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
                                 - 5
               -10
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                         10
                                             15
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                     25
                                      30
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn 75 Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln 90 Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu 105 Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His 120 125 Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg 140 Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu 155 Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr 170 175 His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg 185 190 Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg . 195 200 205 Gln Leu

<210> 448
<211> 154
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1

<400> 448

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu ~50 -55 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -15 -25 -20 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 -5 -Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75 Pro Glu Phe His Ile Glu Ile Leu Ser Ile

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
                 -55
                            -50
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
                -40
                     -35
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
           -25 -20 -15
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
   -10 -5 1
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
5 10
His Pro Cys Ala Thr Tyr Pro Pro Xaa
             25
<210> 450
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 450
Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe Thr
  -25 -20
                                    -15
Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro
              - 5
                                 1
Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile
         10
                         15
Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly
                      30
Phe Asp Leu Asp Met Asp His Thr Ile
<210> 451
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -34..-1
<400> 451
Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser
         -30 -25 -20
Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser
                    -10
       -15
Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys
Ala Ile Ile Leu Met Lys
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<210> 452
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
                           -30
       -35
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
                        -15
                                  -10
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
                     1
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
           15
                            20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
                            35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
                      50
Ala Ile Gly Xaa His Leu Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
                  65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
          80
<210> 453
<211> 166
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
             -30 -25
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                     -15
                             -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
             1 5
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
       15
                20
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
                        35
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
                 50
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
                                  70
              65
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                               85
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Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg

Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu
110 115 120

95 100

Ser Ser Lys Lys Val His 125

<210> 454 <211> 180

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -26..-1

<400> 454

Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly
-25 -20 -15

Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg -10 -5 5

Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 10 15 20

Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe
25 30 35

Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 40 45 50

Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 55 60 65 70

Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu
75 80 85

Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly
90 95 100

Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 105 110 115

Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 120 125 130

Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg 135 140 145 150

Arg Asn Trp Glu

<210> 455

<211> 91

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -64..-1

<400> 455

Met Thr Pro Arg Ile Leu Ser Glu Val Gln Phe Ser Ala Phe Cys Pro
-60 -55 -50

Tyr Trp Thr Ile Ala Arg Ile Leu Glu Arg Val Gly Ser Ala Cys Phe

-45 -40 -35

Arg Leu Glu Leu Cys Ala Ala Ile Val Gly Tyr Phe Val Leu Asp Val
-30 -25 -20

Arg Thr Phe Leu Phe Ile Val Val Cys Val Ile Cys Val Thr Leu Asn

-15 -10 -5
Phe Pro Arg Phe Tyr Phe Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly

Thr Pro Pro Ile Gly Val His Ile Pro Ser Pro

20

25

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Xaa
                         -15
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                 15
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
                               35
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                           50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                        65
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                    80
                                      85
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                95
                                  100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
             110
                              115
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
         125
                           130
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                        145
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
             160
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
       175
                           180 185
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Xaa Leu Pro
           190 195 200
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
         205 210
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
                        225
Xaa
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<210> 457
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 457
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Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro -60 -55 -50 -45

Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -35 -40 Leu Leu Cly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -25 -20 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -10 -5 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 15<sup>.</sup> Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 30 25 Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 45 40 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 90 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 115 105 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 120 125 Glu

<210> 458
<211> 107
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1

<400> 458

 Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg -25
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<210> 459
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1

<400> 459 Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr -5 . Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr 10 15 Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys 25 30 Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr 40 45 Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg 60 Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg 75 Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln 90 Phe Leu Ile Pro Asn Leu Ala Leu Asn

<210> 460 <211> 44 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1

Met Lys Val Gly Val Leu Trp Leu Ile Ser Phe Phe Thr Phe Thr Asp
-15
Gly His Gly Gly Phe Leu Gly Val Ser Trp Cys Tyr Val Ser Tyr Leu
1
5
10
15
Phe Ser Thr Asn Ser Pro Leu Ser Phe Arg Arg Ile

<210> 461 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

<400> 461 Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -5 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 10 15 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 30 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn 40 45 Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His 60 Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

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95 90 95

<211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 462 Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala -35 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -20 -15 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu 1 5 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 15 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 60 65 Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu 95

<210> 463

<210> 462

<211> 232

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -30..-1

<400> 463

Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val
-30 -25 -20 -15

Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa
-10 -5 1

Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu
5 10 15

Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu 20 25 30

Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 35 40 45 50

Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser
55 60 65

Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Gly
70 75 80

Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 85 90 95

Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

```
110
                  105
  100
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
                     125 130
115 120
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
            135 140
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
        150
                155
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
     165 170
                              175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
             185
                              190
Val Lys Cys Lys Phe Leu Tyr Asn
             200
<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arg His Gln Asp Asn Ser Leu Met Phe Phe Ser Met Met
-20 -15 -10
Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
            1 5
Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
  15 20
Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
             35
<210> 465
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 465
Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu
           -15
                          -10
Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro
Gly Arg
  15
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<210> 466 <211> 215 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -54..-1 <400> 466 Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -50 -45 -40 Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu -35 -30 -25 Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -20 -15 -10 Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp -5 1 5 Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser 20 15 Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met 35 30 Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 65 Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 80 Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu 100 105 95 Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 110 115 Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr 130 135 125 Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile 140 145 Ile Ile Arg Lys Cys Phe Ile <210> 467

<210> 468 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1 <400> 468 Met Cys Ser His Ala Ser Met Ser Phe His Thr Leu Phe His Leu Leu -10

Phe Leu Pro His Tyr Ile Glu Thr Phe Lys Pro Gln Ser Lys His Cys

Phe Phe Trp Ile Ala Ala Phe Leu Thr Ser Leu Leu Thr Pro Gln Ser 1

Leu Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe 25

Pro Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa 55

Tyr Trp Asp Asn Leu 60

<210> 469 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 469 Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala -10 -5 Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu 10 Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu 25 20 Pro Asn Phe 35

-10 -5 1 5
Lys His Ser Ile Gln Lys Asn Cys Met Xaa Leu Val Leu Gly Lys Leu
10 15 20

Leu Ser Gln

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -15..-1 <400> 471 Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu -10 -5 Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg 10 Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser 25 Thr Gln His Arq Arq Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala 35 40 <210> 472 <211> 179 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1 <400> 472 Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His -50 Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu -35 -30 Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile -25 -20 -15 Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala -10 -5 1 Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly 10 15 Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile 30 Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa 45 Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser 60 65 His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro 80 Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys 90 95 Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly 110 Gln Val Asn 120 <210> 473

<211> 238 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -71..-1 WO 99/31236 -337- PCT/IB98/02122

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<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
        -65
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
                 -50
                                  -45
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
             -35
                               -30
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
          -20
                           -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
                       1
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
                                  20
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
                               35
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
                   80
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
          95 100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
            110 115 120
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
       125 130 135
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
                       145
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
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<210> 474 <211> 178 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1 <400> 474

Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe -30 -25 Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile -15 -10 Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe 5 Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu 20 Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val 35 Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn 5.5 Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln 70 His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

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100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
 110 115 120
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
125 130
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
-20 -15
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
-5
               1
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
            35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
45 50
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
60 65
                    70
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
          -20 -15 -10
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
      -5 1
                             5
Val Leu Gly Val Phe Phe Pro Ile Leu
 10
             15
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
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<400> 477 Met Arg Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu -20 Leu Phe Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His -5 Ser Glu Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu 15 Arg Trp His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn 30 Cys Ile Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys 45 50 Pro Asn Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys 60 Pro Arg Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr 75 80 Ser

<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 478

Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -15 -10 -5 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 80 85 90 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 110 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 125 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 135 140 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 145 150 155 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 170 160 165 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 195 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215 Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

230

WO 99/31236 -340- PCT/IB98/02122 -

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<210> 479
<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                   ~15
                                        -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
                 1
Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
         15
                            20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                         35
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                     50
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
             80
                               85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
                                    105
         95 100
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
      110
              115
Gly Lys Val Lys Ser Phe Lys
                    130
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                       -15
                 -20
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
              -5
                                1
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
              15
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
                     30
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
                 45
                                   50
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
                     65
Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala
                            80
Gly Arg Gln Cln Lys Lys Ile Glu Arg Xaa Xaa Xaa Leu Xaa
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Asn Asn Asn Arg Asp Leu Ser Met Val Arg Met Lys Ser Met Phe Ala 105 110 Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ile Phe 125 130 Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa 140 145 150 Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys 155 160 Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn 175 180 Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln 190 195 Ala Gly Gly Phe Leu Gly Pro Pro Pro Ser Gly Lys Phe Ser 205

<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -92..-1

<400> 481

Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 -65 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -55 -50 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 -30 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -25 -20 -15 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -10 -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 15 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 45 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Ala 95 90 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro 105 110

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

(213) Homo saptens

<221> SIGNAL <222> -39..-1

<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val
-35 -30 -25

Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu
-20 -15 -10

Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val -5 5

Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu

10 20 25

His Thr Wal Lye Cly Thr Pro Phe Gly Thr Pro Asn Gly Lye Ala

His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala  $30 \hspace{1.5cm} 35 \hspace{1.5cm} 40$ 

Arg Leu Leu Thr His Trp 45

<210> 483

<211> 40

<212> PRT

<213> Homo sapiens

<220'>

<221> SIGNAL

<222> -27..-1

<400> 483

Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr
-25 -20 -15

Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
-10 -5 1 5

Leu Ser Leu Arg Ser Ala Met Ser

10

<210> 484

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly
-15 -5

Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys 20 25 30

Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala

Thr

<210> 485

<211> 130

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 485
Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu
                      -45
          -50
Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg
             -35
                              -30
Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile
       -20 -15
Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr
           1
Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val
                                 20
              15
Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa
            30
Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg
                 50
Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp
               65
Ala Leu
  75
<210> 486
<211> 209
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -84..-1
<400> 486
Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu
                               -75
Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr
                           -60
Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly
                       -45
Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu
                            -25
                    -30
  -35
Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu
-20 -15 -10
Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr
                           5
Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly
                       20
Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val
                    35
Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His
                                  55
                 50
45
Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa
           65
```

Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg

Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

```
100
                                          105
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
           115
                             120
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
    -15 -10
                                  -5
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                         10
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
         -25 -20 -15
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
        -10
                          -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
                   10
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
                -45
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
 -35 -30
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
        -15
                          -10
Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala
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Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys Gly Xaa Asn Thr

<210> 491 <211> 218 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -50..-1 <400> 491 Met His His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys -45 -40 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala -30 -25 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly -15 -10 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser 20 25 Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln

Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

40

55 50 Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser 70 Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp 85 90 Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly 100 105 Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp 115 120 Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe 130 135 Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro 145 150 Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln 165 160

<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 492 Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -15 -10 -5 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr 10 Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 20 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 40 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 55 60 65 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 100 105 110 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Gly 130 135 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 155 160 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 185 Ser Val Tyr Leu Gly Arg Ile Val 200

<210> 493 <211> 134 <212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 493
Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly
                                   -10
Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr
                                              10
Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala
                      20
Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile
                   35
                                       40
Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro
          . 50
                                  55
Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg
                               70
Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu
                          85
Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly
                      100
Asp Glu Val Lys Lys Glu
<210> 494
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 494
Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly
                       -10
                            -5
Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn
1
                                   10
Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly
                               25
Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr
Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His
                      55
His Arg Glu Gly Asp
65
<210> 495
<211> 292
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
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<400> 495 Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe -20 Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr -10 Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr 10 Leu Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe Phe Thr 25 Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu 40 45 Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn 60 Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His 75 Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val 90 Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile 105 110 Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser 125 Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu 135 140 Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe 150 155 160 Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu 170 175 Gly Phe Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe 185 190 Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg 200 205 210 Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro 220 225 Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg 235 Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg 250 Lys Lys Gln Glu 260

<210> 496 <211> 122 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -56..-1

 Phe Cys
 Ala Ser
 Phe Pro
 Ser
 Gly
 Xaa
 Leu
 Ser
 Pro
 Pro
 Leu
 Ala
 Leu
 Ser
 Pro
 Pro
 Pro
 Leu
 Pro
 Ser
 Val
 Phe
 Tyr
 Ser
 Cys
 Gly
 Gly
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<211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 497 Met Leu Xaa Leu Ser Arg Ala Thr Lys Xaa Gly Arg Ala Arg Trp Leu -25 -20 Met Pro Val Ile Pro Ala Leu Gln Glu Ala Xaa Ala Gly Gly Ser Arg -5 Gly Gln Glu Phe Glu Thr Ser Leu Ala Asn Met Glu Thr Glu Ala Gly 10 15 Glu Leu Leu Lys Pro Arg Arg Arg Leu Gln

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<210> 497

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-25 -20 -15 -10
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-5 1 5

Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His
10 15 20

Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp 25 30 35
Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe

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Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp

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Asn Val Gly Pro Leu Ile Ile Lys Lys Glu Thr 75 80

<210> 501 <211> 183 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

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<220>

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<222> -15..-1

<400> 502

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-10
-5
1
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Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu 5 10 15

Gln Gly Xaa Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala 20 25 30

His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu 35 40 45

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Xaa Ala

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<211> 183

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<222> -57..-1

<400> 503

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<221> SIGNAL <222> -14..-1

<400> 504

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Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp
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Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe
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Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Leu Cys His Ser
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90
Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys
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Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro
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          125
Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn
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                                           150
Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly
                      160
                                       165
Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp
                 175
                                    180
Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala
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             190
Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe
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                                               215
His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala
                         225
                                            230
Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu
                      240
                                        245
Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu
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<400> 508

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                                     1
Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser
                             15
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Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp
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Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu
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                                  -35
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
           -25
                              -20
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                         -5
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 Pro
 Lys
 Pro
 Glu
 Gln
 Leu
 Asn
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 Ala
 Phe
 His
 Thr
 Cys
 Gly
 Val
 Phe
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 Ser
 Thr
 Leu
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<400> 511

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Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
                          15
Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
                      30
Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
                  45
                                     50
Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
              60
                                  65
Asn Asn Ala Leu Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg
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Gly Asp Asn Pro Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
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Phe Phe Asp Asp Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu
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Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
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Thr Lys Ser Tyr
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Arg Arg Arg Pro Val Leu Leu Ala Gly Leu His Arg Gln Leu Leu Tyr
Ile Thr Ser Phe Val Phe Val Gly Tyr Tyr Leu Leu Lys Arg Gln Asp
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Tyr Met Tyr Ala Val Arg Asp His Asp Met Phe Ser Tyr Ile Lys Ser
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Phe Glu Glu Phe His Pro Val Arg

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                                                                  300
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                                                                  480
                                                                  540
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                                                                 960
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                                                                 120
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                                                                 180
                                                                 240
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atagaaatcc ttaaaaaagt aagccaacaa acagaaaaga caacaacagt gaaattcaac
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